12 Rec'd PCT/PTO 27 JUL 1999

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED / ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371		ATTORNEY'S DOCKET NUMBER P63763US0
		US APPLICATION NO. (If known, see 37 CFR 1.5) 09/341700
INTERNATIONAL APPLICATION NO. PCT/EP98/00497	INTERNATIONAL FILING DATE 30 January 1998	PRIORITY DATE CLAIMED 31 January 1997
TITLE OF INVENTION AN ANTISENSE OLIGONUCLEOTIDE PREPARATION METHOD		
APPLICANT(S) FOR DO/EO/US Karl-Hermann SCHLINGENSIEPEN -and- Wolfgang BRYSCH		

Applicant herein submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information.

1. ☒ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. ☒ This express request to begin national examination procedures (35 U.S.C. 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39(1).
4. ☒ A proper Demand for Internatl. Preliminary Examination was made by the 19th month from earliest claimed priority date.
5. ☒ A copy of the International Application as filed (35 U.S.C. 371(c)(2))
   a. ☒ is transmitted herewith (required only if not transmitted by the International Bureau).
   b. ☒ has been transmitted by the International Bureau.
   c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US)
6. ☐ A translation of the International Application into English (35 U.S.C. 371(c)(2)).
7. ☒ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3))
   a. ☐ are transmitted herewith (required only if not transmitted by the International Bureau).
   b. ☐ have been transmitted by the International Bureau.
   c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
   d. ☒ have not been made and will not be made.
8. ☐ A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
9. ☐ An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).
10. ☐ A translation of the annexes to the Internatl. Preliminary Examination report under PCT Article 36 (35 U.S.C. 371(c)(5)).

Items 11. to 16. below concern other document(s) or information included:

11. ☐ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
12. ☐ An assignment document for recording. A separate cover sheet compliance with 37 CFR 3.28 and 3.31 is included.
13. ☒ A FIRST preliminary amendment.
    ☐ A SECOND or SUBSEQUENT preliminary amendment.
14. ☐ A substitute specification.
15. ☐ A change of power of attorney and/or address letter.
16. ☒ Other items or information:
    International Search Report — EPO
    PCT/IB/304 Form
    PCT/IB/308 Form
    First Page of Publication
    International Preliminary Examination Report — No Annexes

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US APPLICATION NO. (If known, see 37 CFR 1.5)	INTERNATIONAL APPLICATION NO.	ATTORNEY'S DOCKET NUMBER
09/341700	PCT/EP98/00497	P63763US0

17. ■ The following fees are submitted:

				CALCULATIONS	PTO USE ONLY
Basic National Fee (37 CFR 1.492(a)(1)-(5)): Internatl. prelim. examination fee paid to USPTO (37 CFR 1.492 (a) (1)) .. $670.00 No international preliminary examination fee paid to USPTO (37 CFR 1.492 (a) (2)) but international search fee paid to USPTO (37 CFR 1.445(a)(2)) .. $760.00 Neither international preliminary examination fee (37 CFR 1.492 (a) (3)) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO) .... **$970.00** International preliminary examination fee paid to USPTO (37 CFR 1.492 (a) (4)) and all claims satisfied provisions of PCT Article 33(2)-(4) .... $96.00 Search Report prepared by the EPO or JPO (37 CFR 1.492 (a) (5)) .... **$840.00** **ENTER APPROPRIATE BASIC FEE AMOUNT =**				$ 840.00	
Surcharge of $130.00 for furnishing the **oath or declaration** later than ☐ 20 ■ 30 months from the earliest claimed priority date (37 CFR 1.492(e)).				$ 130.00	
Claims	**Number Filed**	**Number Extra**	Rate		
Total Claims	6 - 20 =	-0-	x $18.00	$	
Independent Claims	1 - 3 =	-0-	x $78.00	$	
Multiple Dependent Claim(s) (if applicable)			+ $260.00	$	
TOTAL OF ABOVE CALCULATIONS =				$ 970.00	
Reduction by 1/2 for filing by **small entity**, if applicable. Verified Small Entity statement must also be filed. (Note 37 CFR 1.9, 1.27, 1.28).				$	
SUBTOTAL =				$ 970.00	
Processing fee of $130 for furnishing the **English translation** later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492(f))				$	
TOTAL NATIONAL FEE =				$ 970.00	
Fee of $40.00 for recording the enclosed **assignment** (37 CFR 1.21(h)). Assignment must be accompanied by appropriate cover sheet (37 CFR 3.28, 3.31).				$	
TOTAL FEES ENCLOSED =				$ 970.00	
				Amt. to be refunded:	$
				Amt. charged:	$

a. ■ A check in the amount of $ 970.00 to cover the above fees is enclosed.

b. ☐ Please charge my Deposit Account No. 06-1358 in the amount of $ — to cover the above fees. A duplicate copy of this sheet is enclosed.

c. ■ The Commissioner is hereby authorized to charge my account any additional fees set forth in §1.492 during the pendency of this application, or credit any overpayment to Deposit Account No. 06-1358. A duplicate copy of this sheet is enclosed.

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By [signature] 22769
for William E. Player
Reg. No. 31,409

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant(s): Karl-Hermann SCHLINGENSIEPEN et al

Serial No.: New

Filed: Herewith

For: AN ANTISENSE OLIGONUCLEOTIDE PREPARATION METHOD

PRELIMINARY AMENDMENT TO LESSEN FEES

Assistant Commissioner of Patents
Washington, D.C. 20231

Sir:

Prior to initial examination, please amend the above-identified application as follows:

IN THE CLAIMS

Claim 3, line 1, delete "any one of the claims 1 or 2", insert --claim 1--;

Claim 5, line 1, delete "and/or 4";

Claim 6, line 1, delete "any one of the claims 1 to 5", insert --claim 1--.

REMARKS

The foregoing Preliminary Amendment is requested in order to delete the multiple dependent claims and avoid paying the multiple dependent claims fee.

Early action on the merits is respectfully requested.

Respectfully submitted,

JACOBSON, PRICE, HOLMAN & STERN, PLLC

By KHolman 22769
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An antisense oligonucleotide preparation method

The present invention is related to a method for the preparation of antisense oligonucleotides and to an oligonucleotide or functional or structural analogs or effective derivatives thereof, forming hydrogen bonds with deoxyribonucleic acids (DNA) and/or ribonucleic acids (RNA) or derivatives thereof including, but not limited to the formation of hydrogen bonds with the bases adenine (A), cytosine (C), guanine (G), uracil (U) or thymidine (T) contained in such molecules or forming hydrogen bonds with residues of a particular protein, such a molecule being capable of altering the expression structure or function, of a gene, an RNA molecule or a protein or altering the level of activity of a gene, an RNA molecule or a protein. Furthermore, the present invention is related to such nucleic acid or functional or structural analogs or effective derivatives thereof, coupled or mixed with folic acid, hormones, steroid hormones such as oestrogen, progesterone, corticosteroids, mineralocorticoids, androgens, peptides, proteoglycans, phospholipids, glycolipids and derivatives therefrom.

Furthermore, the invention is related to the use of said nucleic acids or functional or structural analogs or effec-

tive derivatives thereof, for analyzing the functional properties of a particular gene, RNA, or protein by altering its activity, structure, function or altering its expression levels.

Furthermore, the invention is related to antisense nucleic acids, capable of modulating the expression or functional activity of proteins which regulate cell growth leading to augmentation, inhibition or modulation of cell growth or cell proliferation and/or the expansion of primary cells or stem cells, e.g. in culture or in the living organism.

Furthermore, the invention is related to a pharmaceutical composition comprising said nucleic acids or functional or structural analogs or effective derivatives thereof, hybridizing with an area of the messenger RNA (mRNA) or the DNA of a target gene or binding to a particular protein as well as the use of said nucleic acids, structural analogs and derivatives thereof for the manufacturing of a pharmaceutical composition for the treatment of diseases where the alteration of the structure function, activity or expression of a particular target gene, a particular target RNA or a particular target proteins activity leads to a therapeutic benefit related to the effect of the nucleic acid or derivative thereof.

Modulation of the expression of genes, RNA molecules or proteins or of their activity levels with nucleic acids or functional or structural analogs or effective derivatives thereof is a powerful means to study the function of the respective molecules. For example modulation, e. g. knockdown or increase of the expression of a particular protein can lead to the identification of its physiological as well as its pathophysiological roles in cultured cells as well as in living organisms in vivo.

Furthermore, the aberrant expression or overexpression of genes, RNA molecules or proteins, the expression of foreign DNA, RNA or proteins e. g. derived from infectious organisms or the expression of mutated DNA, RNA and proteins is found in a variety of diseases. Downregulation of the expression or the activity of such DNA, RNA and/or proteins can lead to an inhibition of or to the reversal of pathological processes in which the expression of a particular DNA, RNA and/or protein plays a role. However, nucleic acids or derivatives thereof used for downregulation of DNA, RNA and/or protein expression are often ineffective and/or toxic to the cells or the organisms treated with such molecules.

An object of the present invention is to provide a method for designing and preparation of oligonucleotides or derivatives thereof which avoid the drawbacks of prior art, and give a reliable method for preparation of oligonucleotides having increased effectivity and/or reduced toxicity and/or reduced non-selective effects.

The object is attained by a method having the features of claims 1. Preferred embodiments of the method of the invention are those according to claims 2 to 7.

The method of the invention comprises the steps

- of selecting a target nucleic acid, if necessary elucidating its sequence
- generating the antisense oligonucleotide with the proviso that
    - the oligonucleotide comprises at least 8 residues,
    - the oligonucleotide comprises at maximum twelve elements, which are capable of forming three hydrogen bonds each to cytosine bases,

- the oligonucleotide does not contain four or more consecutive elements, capable of forming three hydrogen bonds each with four consecutive cytosine bases (CCCC) within the target molecule or alternatively four or more consecutive elements of GGGG,
- the oligonucleotide does also not contain 2 or more series of three consecutive elements, capable of forming three hydrogen bonds each with three consecutive cytosine bases (CCC) within the target molecule, or alternatively 2 or more series of three consecutive elements of GGG, and
- the ratio between residues forming two hydrogen bonds per residue (2H-bond-R) with the target molecule and those residues forming three hydrogen bonds per residue (3H-bond-R) with the target molecule, is ruled by the following specifications:

$$\frac{\text{3H-bond-R}}{\text{3H-bond-R} + \text{2H-bond-R}} \geq 0.29$$

- and synthesizing the oligonucleotide thus generated in a per se known manner.

The generated antisense oligonucleotide comprises at least 8 residues in order to have sufficient interaction with the target molecule and has preferably up to 30, more preferably up to 24 or most preferred upt to 18 residues. Shorther chain length are preferred over longer ones to increase specifity and/or reduce non-specific effects.

The oligonucleotide comprises at maximum 12 elements which are capable of forming 3 hydrogen bonds each to cytosine bases. In case of generating an oligonucleotide an element is represented by a residue, thus a nucleotide of the oligo-

nucleotide. In cases of generating a derivative an element is considered as a part of the molecule capable of forming hydrogen bonds. It is preferred that the oligonucleotide comprises at maximum 10 and more preferred at maximum 8 elements which are capable of forming 3 hydrogen bonds each to cytosine bases.

The generated antisense oligonucleotide preferably does not contain 4 or more consecutive guanine bases and does also not contain 2 or more series of 3 consecutive guanine bases.

Preferably, the ratio between residues forming 2 hydrogen bonds per residue (2H-bond-R) with their target molecule and those residues forming 3 hydrogen bonds per residue (3H-bond-R):

$$\frac{\text{3H-bond-R}}{\text{3H-bond-R} + \text{2H-bond-R}}$$

is in the range of greater than 0.33 and smaller than 0.86, more preferably smaller than 0.79 and still more preferred smaller than 0.72.

In one embodiment the oligonucleotides generated by the method of the invention are modified for higher nuclease resistance than naturally occurring nucleotides. Methods for synthezing oligonucleotides and derivatives thereof are known in the art, see for exammple "Oligonucleotides and Analogues", F. Eckstein (Ed.), 1991, IRL Press Oxford or "Protocols for Oligonucleotides and Analogs, Synthesis and Properties", Sudhir Agrawal (Ed.), 1993, Humana Press, Totowa, New Jersey.

Oligonucleotides of the invention may also contain RNA and DNA residues within their chains.

The modifications can be made to the bases, the sugars or the linkages of the oligonucleotides. Preferably, the modifications are phosphorothioate (S-ODN) internucleotide linkages, and/or methylphosphonate internucleotide linkages, N'3 -> P5' phosphoramidate linkages, peptide linkages or 2'-methoxyethoxy modifications of the sugar moiety or modifications of the bases. In a preferred embodiment the oligonucleotide has at least two different types of modifications and more preferably at least two different types of internucleotide linkages. In another preferred embodiment the oligonucleotides are linked to or mixed with folic acid, hormones such as steroid hormones or corticosteroids, peptides, proteoglycans, glycolipids, phospholipids or derivatives thereof.

Surprisingly the molecules, obtainable according to the method of the invention could strongly reduce or avoid toxicity and/or non-specific effects of such molecules and/or had significantly higher activity than sequences selected otherwise. Preferably, the molecules according to the invention have the following features: They do not contain four or more consecutive guanosine (N_aGGGGN_b) or inosine (N_aIIIIN_b) residues and the oligonucleotide does not contain two or more series of three or more consecutive guanosine residues ($N_aGGGN_cGGGN_b$) and does not contain two ore more series of three or more consecutive inosine residues ($N_aIIIN_cIIIN_b$) , wherein N_a, N_b, N_c represent indepently oligonucleotides of any sequence having 0 to 20 residues.

In a preferred embodiment the molecule contains a minimum of 10 residues capable of forming either two or three hydrogen bonds per residue. Furthermore, the molecule contains a maximum of 24 consecutive residues linked by phosphorothioate linkages capable of forming either two or three hydrogen bonds per residue. In molecules according to the invention which contain more than 18 residues the additional

linkages preferably consist of methylphosphonate linkages or phosphodiester linkages.

The chemical structures of antisense oligodeoxy-ribonucleotides are given in figure 1.

The chemical structures of antisense oligo-ribonucleotides are given in figure 2. The oligonucleotide is to be understood as a detail out of a longer nucleotide chain.

Of course, the oligonucleotides may be composed of elements of either figures.

In figures 1 and 2, lit. B means an organic base such as adenine (A), guanine (G), cytosine (C), inosine (I), uracil (U) and thymine (T) which are coupled to the deoxyribose. The linkages between the nucleotides are either phosphodiester bonds as in naturally occurring DNA or linkages spacing the nucleotides in such a way to allow hybridization with its target nucleic acid or binding to a protein in order to regulate its activity, such as e.g. phosphorothioate linkages, methylphosphonate linkages, phosphoramidate linkages or peptide linkages.

R_2 and R_3 represent further residues of the oligonucleotide or derivative.

R_4 represents OH or a modification such as a 2'-methoxy ethoxy derivative.

The modifications of the phosphodiester linkage, shown in figures 1 and 2 can be selected from, but are not limited to.

1. Oligodeoxy-ribonucleotides or oligoribionucleotides substituted by

1.1 R1 = O

1.2 R1 = S

1.3. R1 = F

1.4. R1 = CH_3

1.4. R1 = OEt

2. Oligodeoxy-ribonucleotides where R1 is varied at the internucleotide phosphates within one oligonucleotide

$$5'\quad ((\underset{\substack{|\\ R1a}}{B\text{-}p\text{-}})n\ \ (\underset{\substack{|\\ R1b}}{B\text{-}p\text{-}})m)y\ \ (\underset{\substack{|\\ R1c}}{B\text{-}p\text{-}})x$$

where lit. p stands for the phosphodiester or the phosphoramidate linkage, modified by coupling to R1a, R1b or R1c or for a peptide linkage, or for linkages spacing the nucleotides in such a way to allow hybridization with its target nucleic acid or binding to a protein in order to regulate its activity, structure, function or expression level.

where lit. B = any deoxy-ribonucleotide or ribonucleotide , depending on gene sequence according to the invention.

n, m, x, y = integers 0 - 20

Preferred maximal length of the total number of bases is 30.

2.1	R_{1a} = S	$R_{1b}=CH_3$	$R_{1c}=S$
2.2	R_{1a} = S	$R_{1b}=CH_3$	$R_{1c}=O$
2.2	R_{1a} = S	$R_{1b}=O$	$R_{1c}=S$
2.2	R_{1a} = S	$R_{1b}=O$	$R_{1c}=CH_3$
2.3	R_{1a} = CH_3	$R_{1b}=S$	$R_{1c}=CH_3$
2.4	R_{1a} = CH_3	$R_{1b}=S$	$R_{1c}=O$
2.5	R_{1a} = CH_3	$R_{1b}=O$	$R_{1c}=CH_3$
2.6	R_{1a} = CH_3	$R_{1b}=O$	$R_{1c}=S$

2.7	$R_{1a} = O$	$R_{1b}=S$	$R_{1c}=O$
2.8	$R_{1a} = O$	$R_{1b}=S$	$R_{1c}=CH_3$
2.9	$R_{1a} = O$	$R_{1b}=CH_3$	$R_{1c}=O$
2.10	$R_{1a} = O$	$R_{1b}=CH_3$	$R_{1c}=S$

Preferably, the oligonucleotide comprises a minimum of 10 elements and a maximum of 24 elements capable of forming either 2 or 3 hydrogen bonds per element. The oligonucleotides of the invention can have modifications to the base, the sugar or the phosphate moiety. Preferred modifications are phosphorothioate (S-ODN) internucleotide linkages, and/or methylphosphonate internucleotide linkages, N'3 -> P5' phosphoramidate linkages, peptide linkages or 2'-methoxyethoxy modifications of the sugar or modifications of the bases. In a very preferred embodiment the antisense oligonucleotides comprise the sequences 41 to 73, 74 to 106, 154 to 172, 173 to 203, 298 to 380, 476 to 506, 519 to 556 and 597 to 641 of figure 3 and 1273 - 1764 of figure 5. A further aspect of the invention is the use of the oligonucleotides of the invention for the inhibition of the genes p53, rb, junD, junB, TGF-ß1, TGF-ß2 to influence cell proliferation, in particular of primary cell cultures such as liver cells, kidney cells, osteoclasts, osteoblasts and/or keratinocytes and/or cells of the blood lineage, such as bone marrow stem cells, and/or progenitor cells of red and white blood cells and/or organ stem cells.

The Sequences 41 - 73 and/or 74 - 106 and/or 154 - 203 and/or 519 - 556 and/or 597 - 641 and/or 1273 - 1277 and/or 1481 - 1490 and/or 1532 - 1549 and/or 1656 are useful for the treatment and/or prevention of immunosuppressive disorders including, but not limited to immunosuppression in neoplastic diseases - including gliomas and other brain tumors, sarcomas, carcinomas and lymphomas - and/or immunosuppression as side effect from drugs, including, but not limited to side effects from cytotoxic agents and/or immunosuppression in AIDS patients.

In a further embodiment of the invention these sequences are also useful for the treatment and/or prevention of hyoproliferation of normal cells, including, but not limited to immune cells, bone marrow stem cells, endothelial cells, organ stem cells and proliferating cells of the intestine.

The Sequences 41 - 73 and/or 74 - 106 and/or 298 - 380 and/or 476 - 506 and/or 519 - 556 and/or 1273 - 1480 and/or 1596 - 1614 and/or 1657 - 1658 and/or 1690 and/or 1696 - 1712 and/or 1751 and/or 1753 - 1754 and/or 1757 are useful for the treatment and/or prevention of hyperproliferative disorders, including but not limited to brain tumors, sarcomas, carcinomas and lymphomas, restenosis, hyperplasisa, pulmonary fibrosis, angiogenesis and psoriasis.

The Sequences 1278 - 1480 and/or 1491 - 1531 and/or 1582 - 1595 and/or 1615 - 1655 and/or 1691 - 1694 and/or 1697 - 1750 and/or 1759 - 1764 are useful for the treatment and/or prevention of diseases characterised by hyperfunction of the immune system and/or of inflammatory disorders and/or autoimmune disorders, including, but not limited to asthma (molecules according to the invention being applied by inhalation and/or by parenteral routes and/or orally), multiple sclerosis, inflammatory disorders of the intestine, including jejunitis, ileitis and/or colitis, as well as inflammatory disorders characterised by hyperproliferation and/or hyperfunction of cells of the eosinophilic lineage and/or glomerulonephritis and/or rejection of transplants.

The Sequences 476 - 506 and/or 1550 - 1581 and/or 1582 - 1595 and/or 1658 - 1689 and/or 1691 - 1694 and/or 1713 - 1752 are useful for the treatment and/or prevention of diseases associated with cell degeneration, including, but not limited to neurodegeneration, e.g. Alzheimer´s diseases, Parkinson's, ischemic disorders, including myocardial ischemia and/or ischemia of the nervous system, including stroke.

A further aspect of the present invention is a medicament comprising an oligonucleotide according to the invention together with additives. The oligonucleotides of the invention can be used for the preparation of a medicament for the prevention or the treatment of neoplasm, hypoproliferation, hyperproliferation, degenerative diseases, neurodegenerative diseases, ischaemia, disorders of the immune system and/or infectious diseases and can be used for the analysis of gene function or drug target validation.

Molecules according to the invention can be used to study the function of target molecules and their encoded transcription and/or translation products, including RNA molecules and proteins. Downregulations of a protein or nucleic acid molecule using molecules according to the invention can be used to study the function of the molecule. It is also a feature of the invention that molecules according to the invention can be used to study whether modulation of the product has a desired effect, including therapeutic effects and to use this information to develop a different molecule, in order to modulate the function of the protein.

This includes, for example, drug target validation with a molecule according to the invention, in order to answer the question whether development of an agent capable of modulating the structure, function or expression of a potential target molecule, e. g. an agonist or antagonist of the target molecule has desired effect and may e. g. be of therapeutic or diagnostic use.

It is thus also a feature of the invention that molecules according to the invention can be used for drug target validation, including but not limited to studying whether modulation of a protein or nucleic acid molecule has a desired effect, including therapeutic effects and using this information to develop a compound, e. g. a therapeutic compound capable of modulating the structure, function or

expression of the molecule the function of which was previously studied with molecules according to the invention.

Example 1

Treatment of Peripheral blood mononuclear cells with TGF-ß1 antisense phosphorothioate oligodeoxynucleotides:

Human peripheral blood mononuclear cells (PBMCs) produce transforming growth factor ß1 (TGF-ß1). The TGF-ß1 produced by these cells negatively regulates immune cell proliferation in an autologous manner. This autologous negative regulation of immune cell proliferation could be reversed by antisense TGF-ß1 molecules according to the invention, leading to stimulation of immune cell proliferation. In contrast to the molecules according to the invention, antisense molecules chosen conventionally, including that published by Hatzfeld et al. (1991) did not stimulate immune cell proliferation. Even more surprising, several sequences, chosen conventionally, even reduced immune cell proliferation.

Peripheral blood mononuclear cells (PBMCs) were isolated from venous blood of healthy donors by mixing with an equal volume of RPMI 1640 medium (Gibco) supplemented with 10 % fetal calf serum and 1 mM L-glutamine, followed by layering onto Ficoll-Hypaque (Pharmacia) gradients and centrifugation at 400 g for 30 min. PBMCs were removed from the plasma-Ficoll interface and washed in the above medium. Cells (2 x 104 in 100 μl of medium) were plated into 96 well flat-bottom microtiter plates (Nunc) in serum supplemented complete medium. Cells were activated with 3 μg/ml phytohemagglutinin and incubated with either no oligodeoxynucleotide (untreated control cells) or with 8 μM of different antisense phosphorothioate oligodeoxynucleotides, complementary to different regions of the human TGF-ß1 mRNA for 4 days. Cells were then stained with trypan blue to determine cell viability and counted in a Neubauer counting chamber.

Oligonucleotide sequences were either 33 sequences according to the invention, named sequences TGF-ß1-1 - TGF-ß1-33 or the TGF-ß1 antisense sequence from Hatzfeld et al. (1991), J. Exp. Med., 174, pp. 925 - 929 or 39 other conventionally chosen antisense sequences complementary to human TGF-ß1 mRNA, named N1 - N39 (see figure 3).

Surprisingly the molecules according to the invention were much more effective than antisense TGF-ß1 molecules that were chosen conventionally.

Sequences TGF-ß1-1 - TGF-ß1-33 (see figure 3) enhanced lymphocyte proliferation to between 135 and 213% of untreated controls. In contrast, treatment with the antisense sequence from document Hatzfeld et al. reduced proliferation to 62,8%.

Cells treated with the conventionally chosen TGF-ß1 antisense sequences N1 - N39 surprisingly not only failed to increase lymphocyte proliferation, but several of these sequences even revealed a marked inhibition of cell proliferation to between 51,4% and 77% of controls (sequences N1- N14, N20, N26 and N30 - N39). The antisense TGF-ß1 sequences N15 - N19, N21 - N25, N28 and N29 showed neither significant enhancement nor significant inhibition of cell proliferation with values between 94% and 103%. Sequence N27 showed slight toxicity with a reduction in cell proliferation to 88%.

Inhibition of cell proliferation by some of the TGF-ß1 sequences suggests that they may not be merely ineffective, but also toxic. Analysis of the 26 sequences N1- N14, N20, N26 and N30 - N39 revealed that 23 of them contained either 2 or more sequence motifs with three consecutive Gs (hereafter called GGG motif) or at least one motif with 4, 5, or 6 Gs (motifs GGGG, GGGGG, or GGGGGG). Analysis of the sequence from Hatzfeld et al., which also inhibited PBMC proliferation, surprisingly showed that it too contains a GGGGG plus a GGG motif. The 3 toxic sequences that contained

neither 2 GGG motifs nor a motif of 4 or more consecutive Gs, i.e. sequences N8, N26, and N35 were found have a base content with 11 - 13 G-bases per sequence.

In contrast to the sequences from Hatzfeld et al., N1- N14, N20, N26 and N30 - N39 the sequences TGF-ß1-1 - TGF-ß1-33 showed a G-content of maximally 6 G-bases, no combination of two GGG motifs within a single sequence and no GGGG, GGGGG or GGGGGG motif. Since the TGF-ß1 mRNA contains more than 85 target regions for a GGG antisense motif and more than 34 target regions for a GGGG antisense motif, this finding in the sequences according to the invention was highly unlikely on a statistical basis.

The non-effective sequences N15 - N19, N21 - N25, N28 and N29 were found to contain a different base content from both the toxic and the effective sequences: They content of the bases A and T taken together (A/T-content) ranged from 14,3% to 28,5%. These sequences neither enhanced nor did they inhibit PBMC proliferation. Thus, they appeared to be neither effective nor toxic. In contrast to these non-effective sequences with an A/T content of 14,3% - 28,5%, the effective sequences TGF-ß1-1 - TGF-ß1-33 were found to have an A/T content of between 33% - 71,4%.

A further difference between the sequences of the invention and two thirds of the other sequences was found with respect to non-specific protein binding: Sequences from document Hatzfeld et al. and N1- N14, N20, N26 and N30 - N39 were found to show markedly enhanced non-specific protein binding compared to the sequences of the invention.

Sequences from Hatzfeld et al. (H) and N1 - N39 are shown in figure 3 as well as TGF-ß1 antisense sequences according to the invention.

The finding that, while the sequences TGF-ß1-1 - TGF-ß1-33 stimulated proliferation of PBMC immune cells, the sequence from Hatzfeld et al. and sequences N1- N39 where either non-effective with little alteration in PBMC proliferation or had toxic effects and inhibited PBMC proliferation was extended to further antisense sequences both of TGF-ß2 and other genes as detailed in the following examples 2 - 7.

The sequences of the oligonucleotides related with TGF-ß1 are listed in figure 3 for the sake of ease of readability.

For certain applications, including, but not limited to application in dividing cells, including tumor cells, nucleic acid or functional or structural analogs or effective derivatives thereof according to the invention were coupled to folic acid, either at one of the carboxy-groups or at one of the nitrogen atoms of the folic acid.

Furthermore, for certain applications, nucleic acid or functional or structural analogs or effective derivatives thereof according to the invention are mixed with and/or coupled to hormones, steroid hormones such as oestrogen, progesterone, corticosteroids, mineralocorticoids, androgens, phospholipids, peptides, proteoglycans, glycolipids and derivatives therefrom. Preferably, a coupling occurs at R^2 and/or R^3 of figures 1 and 2.

Example 2

p53 antisense nucleic acids (figure 3 shows the respective oligonucleotides)

p53 is a tumor suppressor gene that negatively regulates cell proliferation. Certain mutations in the gene can alter the function of p53 in such a way that it becomes an oncogene. The effects of p53 antisense oligodeoxynucleotides on cells

containing wild type p53 was analyzed and subsequently also the effect of these sequences on cells with mutated p53.

In cells with wild type p53 effective antisense nucleic acids will lead to downregulation of the wild type p53 protein and thus to enhanced proliferation of the treated cells. Molecules according to the invention are named p53-1 - p53-33. Noneffective p53 antisense sequences were named p53-N-1 - p53-N-18. Toxic sequences, which inhibited proliferation instead of enhancing it as do effective p53 antisense sequences were named p53-T-1 - p53-T-29.

Normal human fibroblasts were grown in RPMI medium supplemented with 5% fetal calf serum (FCS) and 2500 cell/well were plated into 96-well microtiter plates. Antisense phosphorothioate oligonucleotides were added at 2 μM concentration after 2 h.

Two assays to determine cell proliferation were performed:

- To determine 3H-thymidine incorporation, cells were incubated before harvesting with 0,15 μCi 3H-thymidine/well for 6 h. Cells were lysed by freezing , spotted onto glass filters and the amount of incorporated tritium was determined by liquid scintillation counting.
- To determine cell number, cells were stained with trypan blue and counted in a Neubauer counting chamber.

Surprisingly, only treatment of cells with antisense sequences according to the invention (p53-1 - p53-33) resulted in an increase in thymidine incorporation to between 3- and 9-fold.

In contrast, treatment with noneffective sequences (p53-N-1 - p53-N-18) did not result in significant alterations in thymidine incorporation.

Furthermore, treatment with toxic antisense p53 sequences (p53-T-1- p53-T-29) resulted in a decrease in proliferation instead of an increase.

In summary, the 33 antisense sequences according to the invention resulted in effective downregulation of negative growth control by p53 and increased cell proliferation, while the 47 other antisense sequences had either no significant effect on cell proliferation or even suppressed cell proliferation.

Example 3

junB antisense nucleic acids (figure 3 shows the respective oligonucleotides)

junB and junD, two genes encoding transcription factors of the jun gene family are negative regulators of cell growth, like p53. The effects of different junB and junD antisense oligodeoxynucleotides was analyzed.

Effective junB and JunD antisense nucleic acids will lead to downregulation of the JunB an JunD proteins respectively and thus to enhanced proliferation of the treated cells. Antisense molecules according to the invention are named JunB-1 - JunB-19 and JunD-1 - JunD-31. Noneffective junB antisense sequences were named JunB-N-1 - JunB-N-57. Toxic sequences, which inhibited proliferation instead of enhancing it were named JunB-T-1- JunB-T-20 and JunD-T-1 - JunD-T-17.

Normal human fibroblasts were grown in RPMI medium supplemented with 5% fetal calf serum (FCS) and 2500 cell/well were plated into 96-well microtiter plates. Antisense phosphorothioate oligonucleotides were added at 2 μM concentration after 2 h.

Two assays to determine cell proliferation were performed:

- To determine 3H-thymidine incorporation, cells were incubated before harvesting with 0,15 µCi 3H-thymidine/well for 6 h. Cells were lysed by freezing, spotted onto glass filters and the amount of incorporated tritium was determined by liquid scintillation counting.
- To determine cell number, cells were stained with trypan blue and counted in a Neubauer counting chamber.

Surprisingly, again only treatment of cells with antisense sequences according to the invention (JunB-1 - JunB-19 and JunD1- JunD31) resulted in an increase in thymidine incorporation to between 2- and 7-fold.

In contrast, treatment with noneffective sequences (JunB-N-1 - JunB-N-57) did not result in significant alterations in thymidine incorporation.

Furthermore, treatment with toxic antisense junB or JunD sequences (JunB-T-1- JunB-T-20 and JunD-T-1 - JunD-T-17) resulted in a decrease in proliferation instead of an increase.

In summary, the 50 antisense sequences according to the invention resulted in effective downregulation of negative growth control by JunB and JunD , while the 94 other antisense sequences had either no significant effect on cell proliferation or were even toxic.

Example 4 (figure 3 shows the respective oligonucleotides)

erbB-2, is a transmembrane molecule with an intracellular tyrosine kinase activity that is amplified and/or overexpressed by carcinoma cells in a variety of neoplasms including breast cancer, lung cancer, oesophageal and gastric

cancer, bile duct carcinoma, bladder cancer, pancreatic cancer and ovarian cancer.

In several of these tumors, an amplification and overexpression of the c-erbB-2 gene in the tumor tissue has been shown to correlate with a poor clinical prognosis. Overexpression of p185erbB-2 in non-small-cell lung carcinoma has been shown to impart resistance to a number of chemotherapeutic agents.

Effective erbB-2 antisense nucleic acids will lead to downregulation of the erbB-2 protein and in overexpressing tumor cell lines will lead to reduced cell proliferation of the treated cells. Antisense molecules according to the invention are named erbB-2-1 - erbB-2-83. Noneffective erbB-2 antisense sequences were named erbB-2-N-1 - erbB-2-N-95.

erbB-2 overexpressing SK-Br-3 human mammary carcinoma cells were grown in RPMI medium supplemented with 5% fetal calf serum (FCS) and 2500 cell/well were plated into 96-well microtiter plates. Antisense phosphorothioate oligonucleotides were added at 2 μM concentration after 2 h.

To determine erbB-2 protein expression cells were harvested with a cell scraper and subjected to ELISA protein determination.

Only treatment of cells with antisense sequences according to the invention (erbB-2-1 - erbB-2-83) resulted in a significant reduction in erbB-2 protein expression by 40-95%.

In contrast, treatment with noneffective sequences (erbB-2-N-1 - erbB-2-N-95) did not result in significant alterations in erbB-2 protein expression.

To determine cell number, cells were stained with trypan blue and counted in a Neubauer counting chamber.

Only treatment of cells with antisense sequences according to the invention (erbB-2-1 - erbB-2-83) resulted in a reduction in cell number by 35-70%.

In contrast, treatment with noneffective sequences (erbB-2-N-1 - erbB-2-N-95) did not result in significant alterations in cell proliferation.

erbB-2 antisense sequences were shown in figure 3-8 to 3-11

Example 5 (figure 3 shows the respective oligonucleotides)

The c-fos gene encodes an immediate early gene type transcription factor. Effective c-fos antisense nucleic acids will lead to downregulation of the c-Fos protein.

Antisense molecules according to the invention are named c-fos-1 - c-fos-31. Noneffective c-fos antisense sequences were named c-fos-N-1 - c-fos-N-12.

Normal human fibroblasts were grown in RPMI medium supplemented with 5% fetal calf serum (FCS) and 2500 cell/well were plated into 96-well microtiter plates. Antisense phosphorothioate oligonucleotides were added at 2 μM concentration after 2 h.

Expression of the c-Fos protein was determined by ELISA in cell lysates.

Only treatment of cells with antisense sequences according to the invention (c-fos-1 - c-fos-31) resulted in a significant reduction in c-fos protein expression by 45-95%.

In contrast, treatment with noneffective sequences (c-fos-N-1 - c-fos-N-12) did not result in significant alterations in c-Fos protein expression.

Example 6 (figure 3 shows the respective oligonucleotides)

TGF-ß2, like TGF-ß1 is a member of the transforming growth factor-ß family of cytokines.

Overexpression of TGF-ß1 and TGF-ß2 is linked to malignant progression, immunosuppression and escape of the tumors from surveillance by the immune system.

Effective TGF-ß2 antisense nucleic acids will lead to downregulation of the TGF-ß2 growth factor.

Antisense molecules according to the invention are named TGF-ß2-1 - TGF-ß2-38. Noneffective TGF-ß2 antisense sequences were named TGF-ß2-N-1 - TGF-ß2-N-40.

TGF-ß2 overexpressing tumor cells were grown in RPMI medium supplemented with 5% fetal calf serum (FCS) and 2500 cell/well were plated into 96-well microtiter plates. Antisense phosphorothioate oligonucleotides were added at 2 μM concentration after 2 h.

TGF-ß2 protein expression was determined by ELISA, both in the supernatant and in cell lysates.

Only treatment of cells with antisense sequences according to the invention (TGF-ß2-1 - TGF-ß2-38) resulted in a significant reduction in TGF-ß2 protein expression by 35-80%.

In contrast, treatment with noneffective sequences (TGF-ß2-N-1 - TGF-ß2-N-40) did not result in significant alterations in TGF-ß2 protein expression.

Example 7 (figure 3 shows the respective oligonucleotides)

rb antisense nucleic acids
rb is a tumor suppressor gene that negatively regulates cell proliferation. The effects of rb antisense oligodeoxynucleotides on cells containing wild type rb was analyzed.

In cells with wild type rb effective antisense nucleic acids will lead to downregulation of the wild type rb protein and thus to enhanced proliferation of the treated cells. Molecules according to the invention are named rb-1 - rb-45. Noneffective rb antisense sequences were named -1 - rb-N-168. Toxic sequences, which inhibited proliferation instead of enhancing it as do effective rb antisense sequences were named rb-T-1- rb-T-16.

Normal human fibroblasts were grown in RPMI medium supplemented with 5% fetal calf serum (FCS) and 2500 cell/well were plated into 96-well microtiter plates. Antisense phosphorothioate oligonucleotides were added at 2 μM concentration after 2 h.

Two assays to determine cell proliferation were performed:

- To determine 3H-thymidine incorporation, cells were incubated before harvesting with 0,15 μCi 3H-thymidine/well for 6 h. Cells were lysed by freezing , spotted onto glass filters and the amount of incorporated tritium was determined by liquid scintillation counting.
- To determine cell number, cells were stained with trypan blue and counted in a Neubauer counting chamber.

Surprisingly, only treatment of cells with antisense sequences according to the invention (rb-1 - rb-45) resulted in an increase in thymidine incorporation to between 2- and 6-fold.

In contrast, treatment with noneffective sequences (rb-N-1 - rb-N-168) did not result in significant alterations in thymidine incorporation.

Furthermore, treatment with toxic antisense rb sequences (rb-T-1- rb-T-16) resulted in a decrease in proliferation instead of an increase.

In summary, the 45 antisense sequences according to the invention resulted in effective downregulation of negative growth control by rb and increased cell proliferation, while the 184 other antisense sequences had either no significant effect on cell proliferation or even suppressed cell proliferation.

Example 8

Oligonucleotide sequences according to the invention were synthesized with various different backbone modifications: Exemplary results are given below.

For the sequence
erbB-2-42: CATCTGGAAACTTCCAGATG
the following chemical modifications were tested in erbB-2 overexpressing carcinoma cells:

1. S-ODN erbB-2-42 (i.e. all backbone linkages were thioate modifications).
C-pS-A-pS-T-pS-C-pS-T-pS-G-pS-G-pS-A-pS-A-pS-A-pS-C-pS-T-pS-T-pS-C-pS-C-pS-A-pS-G-pS-A-pS-T-pS-G

2. Me-ODN/S-ODN/Me-ODN erbB-2-42 (i.e. Linkages at the 5´and 3´end were methylphosphonate linkages while linkages in the middle were thioate modifications as follows):

C-pMe-A-pMe-T-pS-C-pS-T-pS-G-pS-G-pS-A-pS-A-pS-A-pS-C-pS-T-pS-T-pS-C-pS-C-pS-A-pS-G-pS-A-pMe-T-pMe-G

or

C-pMe-A-pMe-T-pMe-C-pS-T-pS-G-pS-G-pS-A-pS-A-pS-A-pS-C-pS-T-pS-T-pS-C-pS-C-pS-A-pS-G-pMe-A-pMe-T-pMe-G

or

C-pMe-A-pMe-T-pMe-C-pMe-T-pS-G-pS-G-pS-A-pS-A-pS-A-pS-C-pS-T-pS-T-pS-C-pS-C-pS-A-pMe -G-pMe-A-pMe-T-pMe-G

or

C-pMe-A-pMe-T-pMe-C-pMe-T-pMe-G-pMe-G-pS-A-pS-A-pS-A-pS-C-pS-T-pS-T-pS-C-pMe-C-pMe-A-pMe-G-pMe-A-pMe-T-pMe-G

3. Me-ODN / S-ODN erbB-2-42 (i.e. Linkages at the 5´ end were methylphosphonate linkages while linkages at the 3´ were thioate modifications as follows):

C-pMe-A-pMe-T-pMe-C-pMe-T-pMe-G-pMe-G-pMe-A-pMe-A-pMe-A-pS-C-pS-T-pS-T-pS-C-pS-C-pS-A-pS-G-pS-A-pS-T-pS-G

4. S-ODN / Me-ODN erbB-2-42 (i.e. Linkages at the 5´ end were methylphosphonate linkages while linkages at the 3´ were thioate modifications as follows):

C-pS-A-pS-T-pS-C-pS-T-pS-G-pS-G-pS-A-pS-A-pS-A-pMe-C-pMe-T-pMe-T-pMe-C-pMe-C-pMe-A-pMe-G-pMe-A-pMe-T-pMe-G

5. Me-ODN erbB-2-42 (i.e. linkages methylphosphonate linkages):

C-pMe-A-pMe-T-pMe-C-pMe-T-pMe-G-pMe-G-pMe-A-pMe-A-pMe-A-C-pMe-T-pMe-T-pMe-C-pMe-C-pMe-A-pMe-G-pMe-A-pMe-T-pMe-G

6. pN/S-ODN/pN erbB-2-42 (i.e. Linkages at the 5´and 3´end were phosphoramidate linkages while linkages in the middle were thioate modifications as follows):

C-pN-A-pN-T-pS -C-pS-T-pS-G-pS-G-pS-A-pS-A-pS-A-pS-C-pS-T-pS-T-pS-C-pS-C-pS-A-pS-G-pS-A-pN-T-pN-G

or

C-pN-A-pN-T-pN-C-pS-T-pS-G-pS-G-pS-A-pS-A-pS-A-pS-C-pS-T-pS-T-pS-C-pS-C-pS-A-pS-G-pN-A-pN-T-pN-G

or

C-pN-A-pN-T-pN-C-pN -T-pS-G-pS-G-pS-A-pS-A-pS-A-pS-C-pS-T-pS-T-pS-C-pS-C-pS-A-pN -G-pN-A-pN-T-pN-G

or

C-pN-A-pN-T-pN-C-pN -T-pN -G-pN -G-pS-A-pS-A-pS-A-pS-C-pS-T-pS-T-pS-C-pN -C-pN-A-pN -G-pN-A-pN-T-pN-G

where
pS stands for substitution of one of the non-bridging oxygen atoms of the backbone linkage with a sulfur atom, while
pMe stands for substitution of one of the non-bridging oxygen atoms of the backbone linkage with a methyl group.
pN stands for a N3´->P5´ phosphoramidate linkage.

Also a combination of linkages $(N\text{-}pS\text{-}N\text{-}pO\text{-}N\text{-}pO\text{-}N)_n\text{-}[pS\text{-}N]_m$ wherein n = 1 - 10 and m = 0 - 6 where N stand for any nucleotide or structural or functional analog or derivative thereof.

While the Me-ODN backbone modification strongly reduced the erbB-2 activity of the erbB-2-42 sequence to less than 20%, backbone modifications 1.-4. had strong erbB-2 inhibitory capacity with an inhibition of erbB-2 protein expression by between 78% and 89% at 2 µM concentration at 48 h after the beginning of treatment of overexpressing carcinoma cells. While the pure S-ODN had the highest suppression capacity with 89%, the Me-ODN/S-ODN/Me-ODN as well as the Me-ODN/S-ODN

and S-ODN/Me-ODN and pN/S-ODN/pN, displayed reduced protein binding and when tested for complement activation, showed reduced complement activation. These characteristics are advantageous for certain applications e.g. intravenous systemic application in vivo.

Example 9

Similar effects were obtained when testing other sequences according to the invention with the above backbone modifications.

Inhibition of TGF-beta-1 gene expression with the effective sequences for TGF-beta-1 according to the invention was highest with S-ODN and the Me-ODN/S-ODN/Me-ODN backbone modifications and lowest with the Me-ODN modification, while protein binding and complement activation were reduced in sequences containing Me-ODN linkages.

Example 10

Surprisingly, effectivity of sequences according to the invention was significantly improved in various cell types by coupling nucleic acids according to the invention to folic acid:

erbB-2 inhibitory capacity which was relatively low after 24 h compared to 48 h with an inhibition of erbB-2 protein synthesis by 24-37% was markedly increased by coupling sequences according to the invention to folic acid to 48-62% at 2 μM concentration 24 h after the beginning of treatment of overexpressing carcinoma cells.

Similar effects were achieved by coupling sequences according to the invention to folic acid derivatives including aminopterin and amethopterin.

Example 11

Surprisingly, effectivity of sequences according to the invention was strongly improved by coupling oligonucleotides according to the invention to cortisol:

Cellular uptake and inhibitory capacity of sequences according to the invention including sequences for TGF-beta-1, TGF-beta-2, c-fos, p53, erbB-2, rb, c-fos, junB, junD, c-jun, MIP-1 alpha, JAK-2, bcl-2 and were markedly increased by coupling cortisol either to the 3´or 5´ hydroxyl groups of oligonucleotide sequences according to the invention.

Example 12

Effectivity of sequences according to the invention was also strongly improved in various cell types by coupling nucleic acids according to the invention to or mixing them with other steroid hormones and their derivatives, including oestrogens, anti-oestrogens, prednisone, prednisolone, androgens, anti-androgens, gestagenes like progesterone as well as peptides, proteoglycans, glycolipids, phospholipids and derivatives therefrom.

Androgens, particularly androstendion and testosterone, as well as anti-androgens, including cyproteronacetate, flutamide, anandrone, linked to the nucleic acids increased effectiveness of the molecules in various cell types including prostatic carcinoma cells.

Oestrogens, anti-oestrogens and their derivatives, including fosfestrol, toremifen, ethinyloestradiole, diethylstilboestole and the oestradiole derivatives oestradiol-benzoate, oestradiol-valerinate and oestradiol-undecylate, as well as progesterone and its derivatives, including medroxyprogesteroneacetate and megestrolacetate linked to the oligonucleotides strongly enhanced activity of the molecules according

to the invention in various cell types including mammary carcinoma cells.

Claims

1. A method for the preparation of an antisense oligonucleotide or derivative thereof comprising the steps of
   - selecting a target nucleic acid, if necessary elucidating its sequence
   - generating the antisense oligonucleotide with the proviso that
     - the oligonucleotide comprises at least 8 residues,
     - the oligonucleotide comprises at maximum twelve elements, which are capable of forming three hydrogen bonds each to cytosine bases,
     - the oligonucleotide does not contain four or more consecutive elements, capable of forming three hydrogen bonds each with four consecutive cytosine bases (CCCC) within the target molecule or alternatively four or more consecutive elements of GGGG,
     - the oligonucleotide does also not contain 2 or more series of three consecutive elements, capable of forming three hydrogen bonds each with three consecutive cytosine bases (CCC) within the target molecule, or alternatively 2 or more series of three consecutive elements of GGG, and
     - the ratio between residues forming two hydrogen bonds per residue (2H-bond-R) with the target molecule and those residues forming three hydrogen bonds per residue (3H-bond-R) with the target molecule, is ruled by the following specifications:

$$\frac{\text{3H-bond-R}}{\text{3H-bond-R} + \text{2H-bond-R}} \geq 0.29$$

   - and synthesizing the oligonucleotide thus generated in a per se known manner.

2. The method according to claim 1, wherein the generated oligonucleotide complies with the following specification

$$\frac{\text{3H-bond-R}}{\text{3H-bond-R} + \text{2H-bond-R}} = 0.33 \text{ to } 0.86$$

3. The method according to any one of the claims 1 or 2, wherein the generated oligonucleotides are modified for higher nuclease resistance than naturally occurring oligo- or polynucleotides.

4. The method according to claim 3, wherein the generated oligonucleotides are modified at the bases, the sugars or the linkages of the oligonucleotides, preferably by phosphorothioate (S-ODN) internucleotide linkages, and/or methylphosphonate internucleotide linkages, N'3 -> P5' phosphoramidate linkages, peptide linkages or 2'-methoxyethoxy modifications of the sugar or modifications of the bases.

5. The method according to claim 3 and/or 4, wherein the oligonucleotide has at least two different types of modifications.

6. The method according to any one of the claims 1 to 5, wherein the oligonucleotides are reacted with folic acid, hormones such as steroid hormones or cortico-steroides or derivatives thereof by linking the oligo-nucleotides covalently to or mixing with folic acid, hormones such as steroide hormones or corticosteroides, peptides, proteoglycans, glycolipids or phospholipids.

7. An antisense oligonucleotide or derivative thereof obtainable according to the method according to any one of the claims 1 to 6 except oligonucleotides represented by Fig. 4.

8. The oligonucleotide or derivative of claim 7, which does not contain four or more consecutive guanosine (N_aGGGGN_b) or inosine (N_aIIIIN_b) residues and the oligonucleotide does not contain two or more series of three or more consecutive guanosine residues ($N_aGGGN_cGGGN_b$) and does not contain two ore more series of three or more consecutive inosine residues ($N_aIIIN_cIIIN_b$) , wherein N_a, N_b, N_c represent indepently nucloetides or oligonucleotides or derivatives thereof having 0 to 20 residues.

9. The oligonucleotide or derivative of claims 7 and/or 8, comprising a minimum of ten elements and a maximum of 24 elements capable of forming either two or three hydrogen bonds per element.

10. The oligonucleotide or derivative according to any one of the claims 7 to 9, having modifications at the bases, the sugars or the phosphate moieties of the oligonucleotides.

11. The oligonucleotide or derivative of any one of the claims 7 to 10, wherein the modifications are phosphorothioate (S-ODN) internucleotide linkages, and/or methylphosphonate internucleotide linkages, N'3 -> P5' phosphoramidate linkages, peptide linkages or 2'-methoxyethoxy modifications of the sugar or modifications of the bases.

12. The oligonucleotide or derivative of any one of the claims 7 to 11 coupled to or mixed with folic acid, hormones, steroid hormones such as oestrogene, progesterone, corticosteroids, mineral corticoids, peptides, proteoglycans, glycolipids, phospholipids and derivatives therefrom.

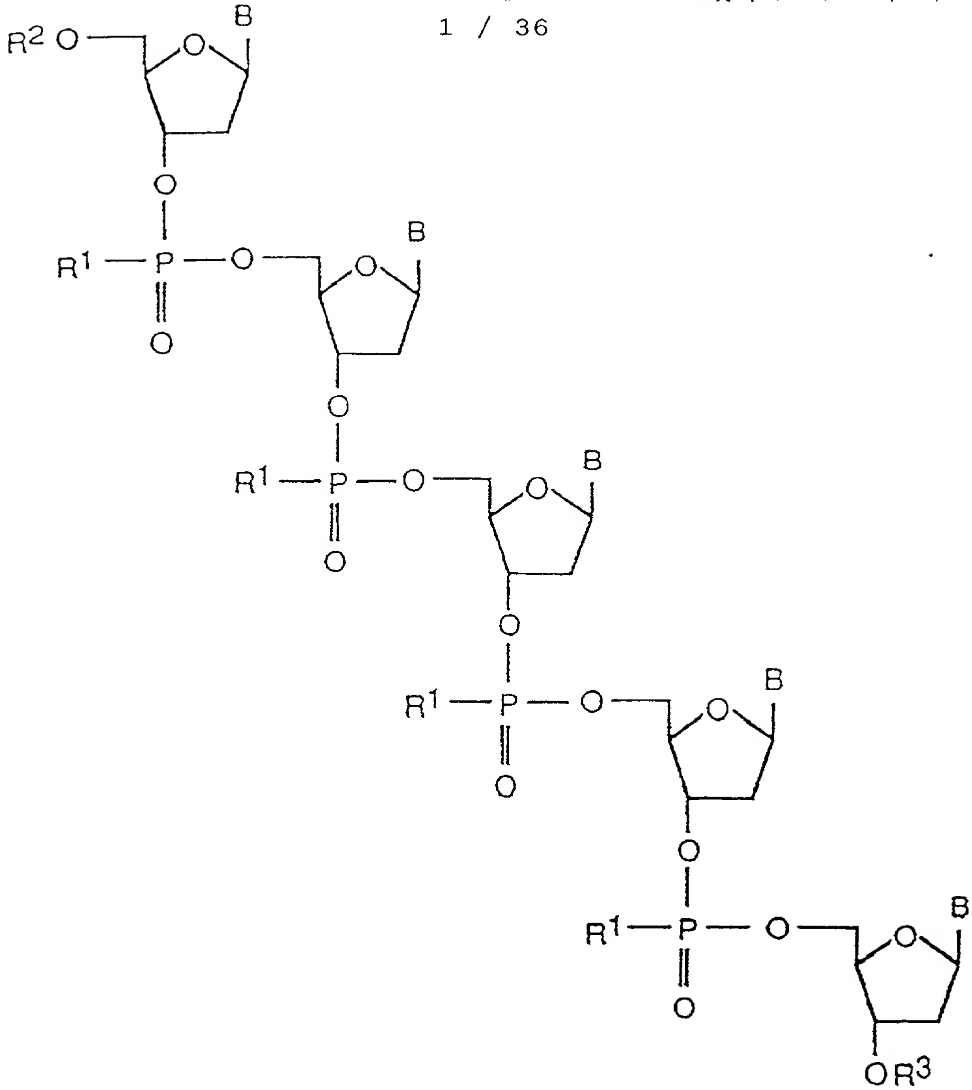
13. The oligonucleotide according to any one of the claims 7 to 12, wherein the antisense oligonucleotide against the TGF-ß1 gene comprise the sequences 41 to 73 of Fig. 3, the oligonucleotides against the gene p53 comprising the sequences 74 to 106 of Fig. 3, the antisense oligonucleotides against junB comprising the sequences 154 to 172 of Fig. 3, the antisense oligonucleotides against junD comprising the sequences 173 to 203 of Fig. 3, the antisense oligonucleotides against the erbB-2 gene comprise the sequences 298 to 380 of Fig 3, the antisense oligonucleotides against c-fos genes comprise the sequences 476 - 506 of Fig. 3; the antisense oligonucleotides against the gene TGF-ß2 comprise the sequences 519 to 556 of Fig. 3 as well as the antisense oligonucleotides against the gene rb comprise the sequences 597 to 641 of Fig. 3.;
as well as sequences 1273 to 1764. of Fig. 5.

14. A composition comprising an oligonucleotide or derivative according to any one of the claims 7 to 13 for the manufacturing of a medicament or a composition for the inhibition of the genes p53, rb, junD, junB, TGF-ß1, TGF-ß2 to influence cell proliferation, in particular of primary cell cultures such as liver cells, kidney cells, osteoclasts, osteoblasts and/or keratinocytes and/or cells of the blood lineage, such as bone marrow stem cells, and/or progenitor cells of red and white blood cells.

15. A medicament comprising an oligonucleotide according to any one of the claims 7 to 13 together with additives.

16. The use of the oligonucleotides according to any of the claims 7 to 13 for the preparation of a medicament for the prevention or the treatment of neoplasm, hypoproliferation, hyperproliferation, degenerative diseases, neurodegenerative diseases, ischaemia, disorders of the immune system and/or infectious diseases, and/or metabolic dysfunctions.

17. The use of the oligonucleotides according to any one of the claims 7 to 13 for the analysis of gene function or drug target validation.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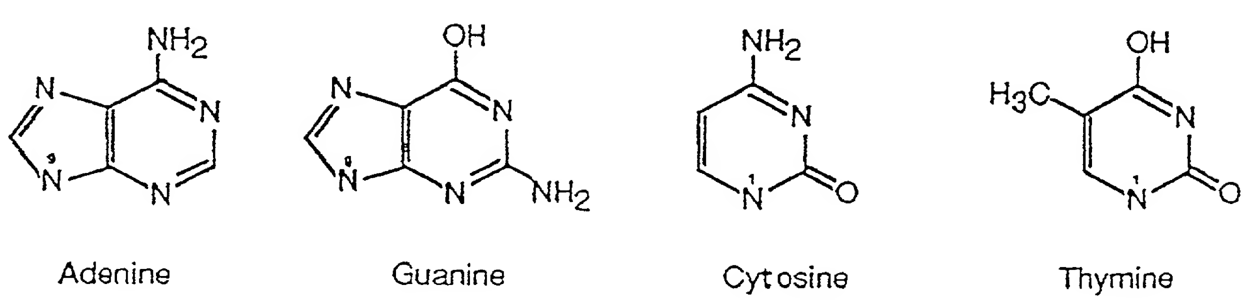
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H3C
Adenine
Guanine
Cytosine
Thymine

Fig. 1

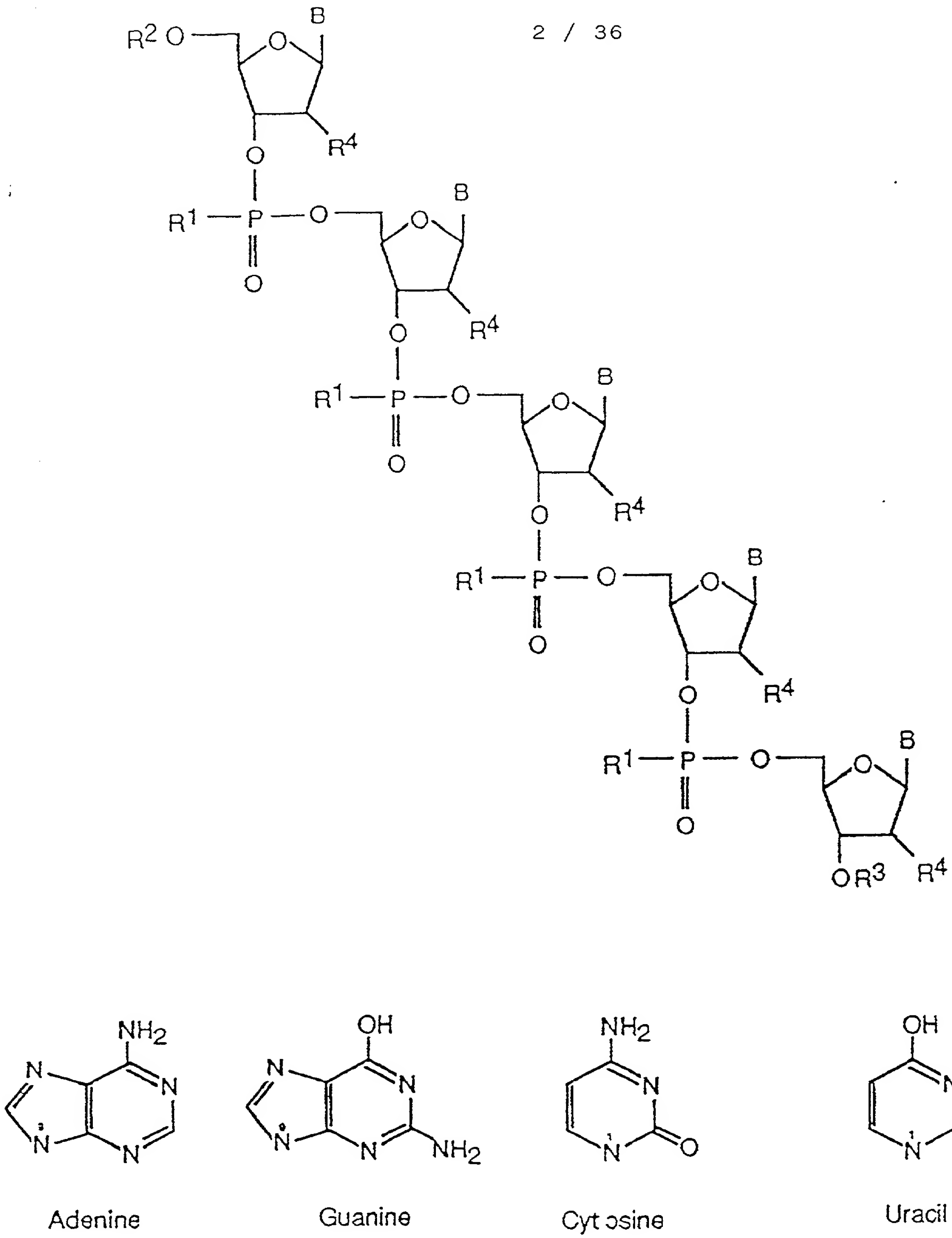

FIG. 2

1.	A3	CCCGGAGGGCGGCATGGGGGA
2.	N1	CCTCAGGGAGAAGGGCGC
3.	N2	GTAGGAGGGCCTCGAGGG
4.	N3	CTGCAGGGGCTGGGGGTC
5.	N4	AGGGCTGGTGTGGTGGGG
6.	N5	GGCATGGGGGAGGCGGCG
7.	N6	CCGGAGGGCGGCATGGGG
8.	N7	GGGGGGCTGGCGAGCCGC
9.	N8	GGACAGGATCTGGCCGCGGATGG
10.	N9	CCCCCTGGCTCGGGGGGC
11.	N10	GGGCCGGGCGGCACCTCC
12.	N11	GGGCAGCGGGCCGGGCGG
13.	N12	ACGGCCTCGGGCAGCGGG
14.	N13	GGGTGCTGTTGTACAGGG
15.	N14	GGGTTTCCACCATTAGCACGCGGG
16.	N15	TCATAGATTTCGTT
17.	N16	TTGTCATAGATTT
18.	N17	AAGAACATATATATG
19.	N18	AAGAACATATATAT
20.	N19	TTGAAGAACATATATA
21.	N20	CCGGGAGAGCAACACGGG
22.	N21	ACTTTTAACTTGA
23.	N22	ATTGTTGCTGTATTT
24.	N23	ATTGTTGCTGTATT
25.	N24	AATTGTTGCTGTATT
26.	N25	AATTGTTGCTGTAT
27.	N26	GGCGAGTCGCTGGGTGCCAGCAGCCGG
28.	N27	GGCGAGTCGCTGGG
29.	N28	ACATCAAAAGATAA
30.	N29	TGACATCAAAAGAT
31.	N30	GGGCCCTCTCCAGCGGGG
32.	N31	GGGCTCGGCGGTGCCGGG
33.	N32	GGGGCAGGGCCCGAGGCA
34.	N33	GGCTCCAAATGTAGGGGC
35.	N34	CGGGTTATGCTGGTTGTACAGGGC
36.	N35	CGGCGCCGCCGAGGCGCCCGGG
37.	N36	GGGGCGGGGCGGGACC
38.	N37	GGGCGGGGCGGGGCGGGG
39.	N38	GGGCGGGGTGGGGCCGGG
40.	N39	GGGCAAGGCAGCGGGGGCGGGG
41.	TGF-ß1-1	CGGTAGCAGCAGCG
42.	TGF-ß1-2	CCAGTAGCCACAGC
43.	TGF-ß1-3	GCAGGTGGATAGTCC
44.	TGF-ß1-4	CTTGCAGGTGGATAG
45.	TGF-ß1-5	CGATAGTCTTGCAGG
46.	TGF-ß1-6	CCATGTCGATAGTCTTGC
47.	TGF-ß1-7	CTCGATGCGCTTCCG
48.	TGF-ß1-8	CCTCGATGCGCTTCC
49.	TGF-ß1-9	GGATGGCCTCGATGC
50.	TGF-ß1-10	GGACAGGATCTGGCC
51.	TGF-ß1-11	CGCAGCTTGGACAGG
52.	TGF-ß1-12	GAGCCGCAGCTTGG
53.	TGF-ß1-13	CGAGCCGCAGCTTG
54.	TGF-ß1-14	ACCTCCCCCTGGCT
55.	TGF-ß1-15	CCACCATTAGCACG
56.	TGF-ß1-16	GAACTTGTCATAGATTTC
57.	TGF-ß1-17	GCTGTGTGTACTCTGC
58.	TGF-ß1-18	GCTCCACGTGCTGC
59.	TGF-ß1-19	GAATTGTTGCTGTATTTC
60.	TGF-ß1-20	GCCAGGAATTGTTGC
61.	TGF-ß1-21	GTGACATCAAAAGATAAC
62.	TGF-ß1-22	GGCTCAACCACTGCC
63.	TGF-ß1-23	GCTGTCACAGGAGC
64.	TGF-ß1-24	CCTGCTGTCACAGG
65.	TGF-ß1-25	GCAGTGTGTTATCCCTGC
66.	TGF-ß1-26	GCAGTGTGTTATCCC

Fig. 3 - 1

67.	TGF-ß1-27	CCAGGTCACCTCGG
68.	TGF-ß1-28	GCCATGAATGGTGGC
69.	TGF-ß1-29	GCCATGAATGGTGG
70.	TGF-ß1-30	CCATGAGAAGCAGG
71.	TGF-ß1-31	GGAAGTCAATGTACAGC
72.	TGF-ß1-32	CCACGTAGTACACGATGG
73.	TGF-ß1-33	GCACTTGCAGGAGC
74.	p53-1	CCATGGCAGTGACC
75.	p53-2	GGCTCCTCCATGGC
76.	p53-3	GCTAGGATCTGACTGC
77.	p53-4	CCTGACTCAGAGGG
78.	p53-5	GGTCTGAAAATGTTTCC
79.	p53-6	CCATTGCTTGGGACGG
80.	p53-7	GCATCAAATCATCC
81.	p53-8	CCATTGTTCAATATCG
82.	p53-9	GGTCTTCAGTGAACC
83.	p53-10	GGAGCTTCATCTGGACC
84.	p53-11	CCTCTGGCATTCTGG
85.	p53-12	AGGGACAGAAGATG
86.	p53-13	GTTTTCTGGGAAGG
87.	p53-14	GGTTTTCTGGGAAG
88.	p53-15	AGGTTTTCTGGGAAG
89.	p53-16	GTAGGTTTTCTGGG
90.	p53-17	GGTAGGTTTTCTGG
91.	p53-18	CCAGAATGCAAGAAGCC
92.	p53-19	GCTGTCCCAGAATGC
93.	p53-20	GCAAGTCACAGACTTGGC
94.	p53-21	CCACAGCTGCACAGG
95.	p53-22	GGTGTGGAATCAACC
96.	p53-23	GTCATGTGCTGTGA
97.	p53-24	CGCTATCTGAGCAGCG
98.	p53-25	CCAGTGTGATGATGG
99.	p53-26	CCAGTAGATTACCACTGG
100.	p53-27	GGCACAAACACGCACC
101.	p53-28	CCACGGATCTGAAGG
102.	p53-29	CGGAACATCTCGAAGCG
103.	p53-30	CCTCATTCAGCTCTCGG
104.	p53-31	CCTTGAGTTCCAAGG
105.	p53-32	CCTTTTTGGACTTCAGG
106.	p53-33	GGAGGTAGACTGACCC
107.	p53-N-1	AAAATGTTTCCT
108.	p53-N-2	TGAAAATGTTTC
109.	p53-N-3	CTGAAAATGTTT
110.	p53-N-4	TCTGAAAATGTTT
111.	p53-N-5	TCTGAAAATGTT
112.	p53-N-6	AAATCATCCATT
113.	p53-N-7	TTGTTCAATATC
114.	p53-N-8	ATTGTTCAATATC
115.	p53-N-9	ATTGTTCAATAT
116.	p53-N-10	CATTGTTCAATAT
117.	p53-N-11	CATTGTTCAATA
118.	p53-N-12	AAAAGTGTTTCT
119.	p53-N-13	ACATGAGTTTTTTAT
120.	p53-N-14	AACATGAGTTTTTTAT
121.	p53-N-15	ACATGAGTTTTTTA
122.	p53-N-16	AACATGAGTTTTTTA
123.	p53-N-17	AACATGAGTTTTTT
124.	p53-N-18	AAAACATCTTGTT
125.	p53-T-1	CAGAGGGGGCTCGACGC
126.	p53-T-2	CTGACTCAGAGGGGGCTC
127.	p53-T-3	AGGGGGACAGAACG
128.	p53-T-4	TTGGGACGGCAAGGGGGACAGAA
129.	p53-T-5	TGGGACGGCAAGGGGGA

Fig. 3 - 2

130.	p53-T-6	GCCACGGGGGGAGCA
131.	p53-T-7	GCAGGGGCCACGGGGGGAG
132.	p53-T-8	AGGGGCCACGGGGG
133.	p53-T-9	CAGGGGCCACGGGG
134.	p53-T-10	GGTGCAGGGGCCACG
135.	p53-T-11	TGGTGCAGGGGCCGCCGG
136.	p53-T-12	GGGGCTGGTGCAGGGGCC
137.	p53-T-13	AGGGGGCTGGTGCAGGGG
138.	p53-T-14	GGGCTGGTGCAGGG
139.	p53-T-15	GAGGGGGCTGGTGCAG
140.	p53-T-16	AGGAGGGGGCTGGTG
141.	p53-T-17	GGGCCAGGAGGGGGCTGG
142.	p53-T-18	AGGGGCCAGGAGGGGGCT
143.	p53-T-19	GGGGCCAGGAGGGG
144.	p53-T-20	CAGGGGCCAGGAGGG
145.	p53-T-21	TCTGGGAAGGGACAGA
146.	p53-T-22	TGAGGGCAGGGGAGTA
147.	p53-T-23	TTGAGGGCAGGGGAG
148.	p53-T-24	CGGGTGCCGGGCGGGGGTG
149.	p53-T-25	CGGACGCGGGTGCCGGGCGGGGGT
150.	p53-T-26	CGGGTGCCGGGCGGG
151.	p53-T-27	GGACGCGGGTGCCGGGCG
152.	p53-T-28	TGGGGGCAGCGCCTCACA
153.	p53-T-29	GGTGGGGGCAGCGCCT
154.	JunB-1	CCATTTTAGTGCACATCCGG
155.	JunB-2	CCATTTTAGTGCACATCC
156.	JunB-3	GCTGTTCCATTTTAGTGC
157.	JunB-4	GTAGTCGTGTAGAG
158.	JunB-5	GTTTGTAGTCGTGTAG
159.	JunB-6	GTTTCAGGAGTTTGTAG
160.	JunB-7	CCAGCTCCGAAGAGG
161.	JunB-8	CGTCGTCGTGATCACG
162.	JunB-9	GGTAAAAGTACTGTCC
163.	JunB-10	GGCTTTGACAAAGCC
164.	JunB-11	CTTGTGCAGATCGTCCAG
165.	JunB-12	CGTGGTTCATCTTGTGC
166.	JunB-13	CACGTGGTTCATCTTGTG
167.	JunB-14	CCTCCTTGAAGGTGG
168.	JunB-15	CGCTCCACTTTGATGCG
169.	JunB-16	CCTTGTCCTCCAGG
170.	JunB-17	GGTACTCGACAGCC
171.	JunB-18	CTGACGTGGGTCATG
172.	JunB-19	CCGTTGCTGACGTGG
173.	JunD-1	CATCCTCCGCCTCC
174.	JunD-2	GTTTCCATCCTCCG
175.	JunD-3	GGTGTTTCCATCCTCC
176.	JunD-4	GGTGTTTCCATCCTC
177.	JunD-5	GCTCAGCGCCTCATC
178.	JunD-6	CCTTCTTCATCATGCTGC
179.	JunD-7	CCTTCTTCATCATGCTG
180.	JunD-8	CCTTCTTCATCATGC
181.	JunD-9	GCGTCCTTCTTCATCATGC
182.	JunD-10	CCTGCTCACTCAGG
183.	JunD-11	CGCAGGCTTGAGCG
184.	JunD-12	GCCAGCTTCAGCAGC
185.	JunD-13	GGTGGTGACCAGCC
186.	JunD-14	CCTCGGCGAACTCC
187.	JunD-15	GCTTGTGTAAATCC
188.	JunD-16	GGTTCTGCTTGTGTAAATCC
189.	JunD-17	GCTGCTCAGGTTCGC
190.	JunD-18	GAAGGCGACCGTCG
191.	JunD-19	CGAAGGCGACCGTC
192.	JunD-20	GCACCGTCTGTGGC
193.	JunD-21	CGTGTCCATGTCGATGG
194.	JunD-22	CGTGTCCATGTCGATG

Fig. 3 - 3

195.	JunD-23	GCGTGTCCATGTCG
196.	JunD-24	CCAGCTTGCGCTTGC
197.	JunD-25	CGCTCCAGCTTGCG
198.	JunD-26	CGTGTTCTGACTCTTGAG
199.	JunD-27	CGTGTTCTGACTCTTG
200.	JunD-28	GCTGTTGACGTGGC
201.	JunD-29	CGACTCAGTACGCC
202.	JunD-30	GCCATGCCCGACTC
203.	JunD-31	CCCTTGGAGGTGGC
204.	JunB-N-1	TTTTAGTGCACAT
205.	JunB-N-2	TGTTCCATTTTAGT
206.	JunB-N-3	AAAAAAAGTGGAAG
207.	JunB-N-4	TACAAAAAAAAGTG
208.	JunB-N-5	ATACAAAAAAAAGT
209.	JunB-N-6	CATACAAAAAAAAGT
210.	JunB-N-7	CATACAAAAAAAAG
211.	JunB-N-8	GAAAAAAAACATAC
212.	JunB-N-9	CAGAAAAAAAACATAC
213.	JunB-N-10	CAGAAAAAAAACAT
214.	JunB-N-11	TTCAATATGAATCG
215.	JunB-N-12	TATTCAATATGAATCG
216.	JunB-N-13	TATTCAATATGAATC
217.	JunB-N-14	TATTCAATATGAAT
218.	JunB-N-15	TATATTCAATATGAA
219.	JunB-N-16	TTATATTCAATATGA
220.	JunB-N-17	TATTATATTCAATATGA
221.	JunB-N-18	TTATATTCAATATG
222.	JunB-N-19	TATTATATTCAATATG
223.	JunB-N-20	ATTATATTCAATAT
224.	JunB-N-21	TATTATATTCAATAT
225.	JunB-N-22	ATATATTATATTCAATAT
226.	JunB-N-23	AAATATATTATATTCAATAT
227.	JunB-N-24	TATTATATTCAATA
228.	JunB-N-25	ATATATTATATTCAATA
229.	JunB-N-26	CAAATATATTATATTCAATA
230.	JunB-N-27	TATATTATATTCAAT
231.	JunB-N-28	AATATATTATATTCAAT
232.	JunB-N-29	TATATTATATTCAA
233.	JunB-N-30	CAAATATATTATATTCAA
234.	JunB-N-31	CAAATATATTATATTCA
235.	JunB-N-32	CAAATATATTATATTC
236.	JunB-N-33	CACAAATATATTATATTC
237.	JunB-N-34	AAATATATTATATT
238.	JunB-N-35	CAAATATATTATATT
239.	JunB-N-36	CAAATATATTATAT
240.	JunB-N-37	CACAAATATATTATAT
241.	JunB-N-38	CACAAATATATTAT
242.	JunB-N-39	TACACAAATATATTAT
243.	JunB-N-40	TACACAAATATATTA
244.	JunB-N-41	TAAATACACAAATATATT
245.	JunB-N-42	AATACACAAATATA
246.	JunB-N-43	GTTAAATACACAAATA
247.	JunB-N-44	TGTTAAATACACAA
248.	JunB-N-45	TTTAGAGACTAAGT
249.	JunB-N-46	ATAAACTCTTTAGA
250.	JunB-N-47	TAAAATAAACTCTTTAG
251.	JunB-N-48	TAAAATAAACTCTTTA
252.	JunB-N-49	TTAAAATAAACTCTTT
253.	JunB-N-50	CTTAAAATAAACTC
254.	JunB-N-51	TAAAAAGAACAAACA
255.	JunB-N-52	TAAAAAGAACAAAC
256.	JunB-N-53	CAATAAAAAGAACAA
257.	JunB-N-54	TCAATAAAAAGAACAA
258.	JunB-N-55	TCAATAAAAAGAAC
259.	JunB-N-56	TTCAATAAAAAGAA
260.	JunB-N-57	TAGATTCAATAAAAAGA

Fig. 3 - 4

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261.	JunB-T-1	TGGCGCGGGCGGGTAGC
262.	JunB-T-2	GGGCTGGCGCGGGCGGGTAG
263.	JunB-T-3	TCGGGGGCTGGCGCGGGCGGG
264.	JunB-T-4	TGGGTGCCTGGTCGCGCGTTCTCGGG
265.	JunB-T-5	AGGGTCCCTGCGGGGCCG
266.	JunB-T-6	GGGAGGGTCCCTGCGGGG
267.	JunB-T-7	GGGAGGGTCCCTGCGG
268.	JunB-T-8	TGGGCCGGGTCCGC
269.	JunB-T-9	TCCCGGGGGTGTAG
270.	JunB-T-10	AGTACTGTCCCGGGGGTGT
271.	JunB-T-11	GGGACACGTTGGGGGGTG
272.	JunB-T-12	GCCGGGGGCCCCCCGGTAGC
273.	JunB-T-13	CGGGCCCAGCCGGGGGC
274.	JunB-T-14	CGGGCCCAGCCGGG
275.	JunB-T-15	GGGAGGTGGCTCCGGGCCGG
276.	JunB-T-16	AGGGCGGCGCGTGTGGGA
277.	JunB-T-17	GGGTGGCCACCGGCGAAGGG
278.	JunB-T-18	AGGGGCAGGGGACGT
279.	JunB-T-19	TAAAGGGGCAGGGGACGT
280.	JunB-T-20	AGGGGGTGTCCGTAAAGGGG
281.	JunD-T-1	GGGGACGCGAACGTGCCGCCG
282.	JunD-T-2	CGGGGAACAAGCGGCCCGGGG
283.	JunD-T-3	GGCCGTCGGGGGCG
284.	JunD-T-4	GCGGCCGTCGGGGGC
285.	JunD-T-5	AGGGGGGTAGGAGGCGGG
286.	JunD-T-6	GCGCTGGGGGCGCC
287.	JunD-T-7	GGCCGTCGGGGGGT
288.	JunD-T-8	GGGGAGGCCAGCTTC
289.	JunD-T-9	GGCCGCCACCTTGGGG
290.	JunD-T-10	GCGGCCGCCGCCGGGG
291.	JunD-T-11	GGGCGCGGCCGCCGCCGGGG
292.	JunD-T-12	GGGGTGGCGGCGGCGG
293.	JunD-T-13	GGGGGTGGCGGCGGC
294.	JunD-T-14	TGGGGCAGCAGCTGGCAG
295.	JunD-T-15	CGGGGCGCCCACGACACC
296.	JunD-T-16	CGGGGCGCCCACGACAC
297.	JunD-T-17	GGGCCGCACCCTCTCCAAGTCCGGGG
298.	ErbB-2-1	GCAGCAGTCAGTGG
299.	ErbB-2-2	CCATTGTCTAGCACGG
300.	ErbB-2-3	GGTCTCCATTGTCTAGC
301.	ErbB-2-4	GGTGGTATTGTTCAGC
302.	ErbB-2-5	GCTGGATCAAGACCC
303.	ErbB-2-6	CCACAAAATCGTGTCC
304.	ErbB-2-7	CCTTCCACAAAATCGTGTCC
305.	ErbB-2-8	GGTTGTTCTTGTGG
306.	ErbB-2-9	CCTCTTGGTTGTGC
307.	ErbB-2-10	CCAGAGTCTCAAACACTTGG
308.	ErbB-2-11	GGTAACCTGTGATCTCTTCC
309.	ErbB-2-12	CCTGCAGTACTCGG
310.	ErbB-2-13	GGCATTCACATACTCC
311.	ErbB-2-14	GCAAACAGTGCCTGGC
312.	ErbB-2-15	CGCATCGTGTACTTCCG
313.	ErbB-2-16	GCACGTTCCGAGCG
314.	ErbB-2-17	GGTACCAGATACTCC
315.	ErbB-2-18	CCAGTGGAGACCTGG
316.	ErbB-2-19	CCTGAGGACACATCAGG
317.	ErbB-2-20	CCTCACTTGGTTGTGAGC
318.	ErbB-2-21	GGAAGATGTCCTTCC
319.	ErbB-2-22	GCACACTGCTCATGGC
320.	ErbB-2-23	GCTGTCACCTCTTGG
321.	ErbB-2-24	CCTCTGCTGTCACC
322.	ErbB-2-25	CCACACATCACTCTGG
323.	ErbB-2-26	CCTCCTCTTCAGAGG

Fig. 3 - 5

324.	ErbB-2-27	CCTTCTGGTTCACACTGG
325.	ErbB-2-28	CATGGTGCTCACTGCG
326.	ErbB-2-29	CTTGGTTGTGAGCG
327.	ErbB-2-30	GGACAGGCAGTCAC
328.	ErbB-2-31	GTCACCTCTTGGTTGTGC
329.	ErbB-2-32	CCAGAGTCTCAAACAC
330.	ErbB-2-33	CACATACTCCCTGG
331.	ErbB-2-34	GACCAGCACGTTCCG
332.	ErbB-2-35	GTTGGTGTCTATCAGTG
333.	ErbB-2-36	CCCTGGTAGAGGTG
334.	ErbB-2-37	CTCAAACACTTGGAGC
335.	ErbB-2-38	CACACATCACTCTGGTGG
336.	ErbB-2-39	GCACAGACAGTGCGC
337.	ErbB-2-40	CATGGCAGCAGTCAG
338.	ErbB-2-41	CTGCTCATGGCAGCAG
339.	ErbB-2-42	CATCTGGAAACTTCCAGATG
340.	ErbB-2-43	CTGGAAACTTCCAG
341.	ErbB-2-44	CATAACTCCACACATCACTC
342.	ErbB-2-45	CACCATAACTCCACACATC
343.	ErbB-2-46	CTGGTGGGTGAACC
344.	ErbB-2-47	CGGATTACTTGCAGG
345.	ErbB-2-48	CGCTAGGTGTCAGCG
346.	ErbB-2-49	GCCATCACGTATGC
347.	ErbB-2-50	GCATACACCAGTTCAGC
348.	ErbB-2-51	CCATCAAATACATCGG
349.	ErbB-2-52	CCAGCAGAAGTCAGG
350.	ErbB-2-53	GCTTCATGTCTGTGC
351.	ErbB-2-54	GGTGAGTTCCAGGTTTCC
352.	ErbB-2-55	CCACAAAATCGTGTCCTGG
353.	ErbB-2-56	CCCTTACACATCGG
354.	ErbB-2-57	GCAGCTCACAGATGC
355.	ErbB-2-58	GCACTGGTAACTGC
356.	ErbB-2-59	CCTGGATATTGGCACTGG
357.	ErbB-2-60	CCAGCAAACTCCTGG
358.	ErbB-2-61	GCAGAAATGCCAGGC
359.	ErbB-2-62	CCATTGTGCAGAATTCG
360.	ErbB-2-63	CCCTGCAGTACTCGG
361.	ErbB-2-64	GGCATTCACATACTCCC
362.	ErbB-2-65	GGTCAGGTTTCACACC
363.	ErbB-2-66	CCAGGTCCACACAGG
364.	ErbB-2-67	CCTTGTCATCCAGG
365.	ErbB-2-68	GGATCCCAAAGACC
366.	ErbB-2-69	CCTCAACACTTTGATGG
367.	ErbB-2-70	GCTGTGTCACCAGC
368.	ErbB-2-71	GGTCTAAGAGGCAGCC
369.	ErbB-2-72	GGCAATCTGCATACACC
370.	ErbB-2-73	CCTGTGTACGAGCC
371.	ErbB-2-74	CCATCCACTTGATGG
372.	ErbB-2-75	CCCACACAGTCACACC
373.	ErbB-2-76	CCATCGTAAGGTTTGG
374.	ErbB-2-77	CCTTTTCCAGCAGG
375.	ErbB-2-78	GGAGAATTCAGACACC
376.	ErbB-2-79	CCAAGTCCTCATTCTGG
377.	ErbB-2-80	CCATCAGTCTCAGAGG
378.	ErbB-2-81	CCTTTGAAGGTGCTGG
379.	ErbB-2-82	GGCATGGCAGGTTCC
380.	ErbB-2-83	CCTGGCATGGCAGG
381.	ErbB-2-N-1	AGATGTATAGGTAA
382.	ErbB-2-N-2	ATTTTCACATTCTC
383.	ErbB-2-N-3	AATTTTCACATTCTC
384.	ErbB-2-N-4	AATTTTCACATTCT
385.	ErbB-2-N-5	GAATTTTCACATTC
386.	ErbB-2-N-6	GGAATTTTCACATT
387.	ErbB-2-N-7	AGATTTCTTTGTTG
388.	ErbB-2-N-8	AAGATTTCTTTGTTG
389.	ErbB-2-N-9	AAGATTTCTTTGTT

Fig. 3 - 6

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390.	ErbB-2-N-10	TAAGATTTCTTTGTT
391.	ErbB-2-N-11	CTAAGATTTCTTTGTT
392.	ErbB-2-N-12	TAAGATTTCTTTGT
393.	ErbB-2-N-13	CTAAGATTTCTTTGT
394.	ErbB-2-N-14	CTAAGATTTCTTTG
395.	ErbB-2-N-15	TCTAAGATTTCTTT
396.	ErbB-2-N-16	GTCTAAGATTTCTTT
397.	ErbB-2-N-17	GTCTAAGATTTCTT
398.	ErbB-2-N-18	TTCGTCTAAGATTT
399.	ErbB-2-N-19	ATTTTGACATGGTT
400.	ErbB-2-N-20	AATTTTGACATGGTT
401.	ErbB-2-N-21	AATTTTGACATGGT
402.	ErbB-2-N-21	TAATTTTGACATGGT
403.	ErbB-2-N-23	TAATTTTGACATGG
404.	ErbB-2-N-24	GTAATTTTGACATG
405.	ErbB-2-N-25	TGTAATTTTGACATG
406.	ErbB-2-N-26	TGTAATTTTGACAT
407.	ErbB-2-N-27	TCTGTAATTTTGACAT
408.	ErbB-2-N-28	CTGTAATTTTGACA
409.	ErbB-2-N-29	TCTGTAATTTTGACA
410.	ErbB-2-N-30	TCTGTAATTTTGAC
411.	ErbB-2-N-31	GTCTGTAATTTTGA
412.	ErbB-2-N-32	AAGTCTGTAATTTTGA
413.	ErbB-2-N-33	AGTCTGTAATTTTG
414.	ErbB-2-N-34	AAGTCTGTAATTTTG
415.	ErbB-2-N-35	AAGTCTGTAATTTT
416.	ErbB-2-N-36	GAAGTCTGTAATTTT
417.	ErbB-2-N-37	GAAGTCTGTAATTT
418.	ErbB-2-N-38	ATGTAGACATCAAT
419.	ErbB-2-N-39	ATCATCCAACATTT
420.	ErbB-2-N-40	AATCATCCAACATTT
421.	ErbB-2-N-41	AATCATCCAACATT
422.	ErbB-2-N-42	ACCATCAAATACAT
423.	ErbB-2-N-43	AAAAACGTCTTTGA
424.	ErbB-2-N-44	TTTTGTTCTTAGACA
425.	ErbB-2-N-45	TTTTGTTCTTAGAC
426.	ErbB-2-N-46	TAAACAGAAAAGCA
427.	ErbB-2-N-47	ACTAAACAGAAAAG
428.	ErbB-2-N-48	AAACTAAACAGAAAAG
429.	ErbB-2-N-49	AACTAAACAGAAAA
430.	ErbB-2-N-50	AAACTAAACAGAAAA
431.	ErbB-2-N-51	AAACTAAACAGAAA
432.	ErbB-2-N-52	TAAAAACTAAACAGAAA
433.	ErbB-2-N-53	AAAACTAAACAGAA
434.	ErbB-2-N-54	GTAAAAACTAAACAGAA
435.	ErbB-2-N-55	AAAAACTAAACAGA
436.	ErbB-2-N-56	TAAAAACTAAACAGA
437.	ErbB-2-N-57	TAAAAACTAAACAG
438.	ErbB-2-N-58	GTAAAAACTAAACA
439.	ErbB-2-N-59	AAAAAGTAAAAACTAAACA
440.	ErbB-2-N-60	AGTAAAAACTAAAC
441.	ErbB-2-N-61	AAAAAAAGTAAAAACTAAAC
442.	ErbB-2-N-62	AAGTAAAAACTAAA
443.	ErbB-2-N-63	AAAAAAAGTAAAAACTAAA
444.	ErbB-2-N-64	AAAGTAAAAACTAA
445.	ErbB-2-N-65	AAAAGTAAAAACTA
446.	ErbB-2-N-66	AAAAAAAGTAAAAACTA
447.	ErbB-2-N-67	AAAAAGTAAAAACT
448.	ErbB-2-N-68	AAAAAAAGTAAAAACT
449.	ErbB-2-N-69	AAAAAAAGTAAAAAC
450.	ErbB-2-N-70	CAAAAAAAGTAAAAAC
451.	ErbB-2-N-71	AAAAAAAGTAAAAA
452.	ErbB-2-N-72	CAAAAAAAGTAAAA
453.	ErbB-2-N-73	AACAAAACAAAAAAAGTAAA
454.	ErbB-2-N-74	AAACAAAAAAAGTA
455.	ErbB-2-N-75	CAAAACAAAAAAAGTA
456.	ErbB-2-N-76	CAAAACAAAAAAAGT

Fig. 3 - 7

457.	ErbB-2-N-77	CAAAACAAAAAAAG
458.	ErbB-2-N-78	CTTTAAAAAAACAAAAC
459.	ErbB-2-N-79	TCTTTAAAAAAACAAA
460.	ErbB-2-N-80	GTCTTTAAAAAAACAAA
461.	ErbB-2-N-81	GTCTTTAAAAAAACA
462.	ErbB-2-N-82	GTCTTTAAAAAAAC
463.	ErbB-2-N-83	TTTATTTCGTCTTT
464.	ErbB-2-N-84	TCTTTATTTCGTCT
465.	ErbB-2-N-85	TATTTGCAAATGGA
466.	ErbB-2-N-86	TATATTTGCAAATGG
467.	ErbB-2-N-87	TATATTTGCAAATG
468.	ErbB-2-N-88	CAAAATATATTTGCAAATG
469.	ErbB-2-N-89	CAAAATATATTTGCAAAT
470.	ErbB-2-N-90	CAAAATATATTTGCA
471.	ErbB-2-N-91	CAAAATATATTTGC
472.	ErbB-2-N-92	TTCCAAAATATATTTG
473.	ErbB-2-N-93	TTTTCCAAAATATATTT
474.	ErbB-2-N-94	GTTTTCCAAAATATATT
475.	ErbB-2-N-95	GTTTTCCAAAATAT
476.	c-fos-1	GGTTAGGCAAAGCC
477.	c-fos-2	CCGAGAACATCATCGTGG
478.	c-fos-3	CCGAGAACATCATCGTG
479.	c-fos-4	CCGAGAACATCATCG
480.	c-fos-5	CGTAGTCTGCGTTGAAGC
481.	c-fos-6	CCATGCTGGAGAAGG
482.	c-fos-7	CCGTGCAGAAGTCC
483.	c-fos-8	GGAATGAAGTTGGC
484.	c-fos-8	TGACCGTGGGAATG
485.	c-fos-10	TGGCAGTGACCGTG
486.	c-fos-11	AGATGGCAGTGACC
487.	c-fos-12	CGAGATGGCAGTGACC
488.	c-fos-13	CCAGCCACTGCAGG
489.	c-fos-14	GCACCAGCCACTGC
490.	c-fos-15	CCCTGGAGTAAGCC
491.	c-fos-16	GGAGATAACTGTTCCACC
492.	c-fos-17	GGAGATAACTGTTCC
493.	c-fos-18	CTTCTAGTTGGTCTG
494.	c-fos-19	CATCTTCTAGTTGG
495.	c-fos-20	TCTCATCTTCTAGTTGG
496.	c-fos-21	CTGCAAAGCAGACTTCTC
497.	c-fos-22	CCTTCAGCAGGTTGG
498.	c-fos-23	CCCAGGTCATCAGG
499.	c-fos-24	CCAGTCAGATCAAGG
500.	c-fos-25	GGTGAAGGCCTCCTC
501.	c-fos-26	CAGGGTGAAGGCCTC
502.	c-fos-27	CCTGGATGATGCTGG
503.	c-fos-28	CCACTGTGCAGAGG
504.	c-fos-29	GGAGTACAGGTGACC
505.	c-fos-30	GCTCATTGCTGCTGC
506.	c-fos-31	GGAAGGCTCATTGCTGC
507.	c-fos-N-1	TTTTCTCTTCTTCT
508.	c-fos-N-2	ATCTTATTCCTTTC
509.	c-fos-N-3	CATCTTATTCCTTT
510.	c-fos-N-4	TAGTTTTTCCTTCT
511.	c-fos-N-5	TCTAGTTTTTCCTT
512.	c-fos-N-6	AACTCTAGTTTTTC
513.	c-fos-N-7	GAACTCTAGTTTTT
514.	c-fos-N-8	TGAACTCTAGTTTTT
515.	c-fos-N-9	ATGAACTCTAGTTTTT
516.	c-fos-N-10	TGAACTCTAGTTTT
517.	c-fos-N-11	ATGAACTCTAGTTTT
518.	c-fos-N-12	ATGAACTCTAGTTT
519.	TGF-ß2-1	GCACACAGTAGTGC

Fig. 3 - 8

520.	TGF-ß2-2	GCAGGATCAGAAAAGC
521.	TGF-ß2-3	GCAGGTAGACAGGC
522.	TGF-ß2-4	GCTTGCTCAGGATCTGC
523.	TGF-ß2-5	GCAAGTCCCTGGTGC
524.	TGF-ß2-6	CCTGGAGCAAGTCC
525.	TGF-ß2-7	CGTAGTACTCTTCGTCG
526.	TGF-ß2-8	CGTAGTACTCTTCG
527.	TGF-ß2-9	GTAAACCTCCTTGG
528.	TGF-ß2-10	GTCTATTTTGTAAACCTCC
529.	TGF-ß2-11	GCATGTCTATTTTGTAAACC
530.	TGF-ß2-12	GGCATCAAGGTACCC
531.	TGF-ß2-13	GGCATCAAGGTACC
532.	TGF-ß2-14	GCTTTCACCAAATTGGAAGC
533.	TGF-ß2-15	GAGAATCTGATATAGCTC
534.	TGF-ß2-16	GGAGATGTTAAATCTTTGG
535.	TGF-ß2-17	GCTGTCGATGTAGC
536.	TGF-ß2-18	CCAGGTTCCTGTCTTTATGG
537.	TGF-ß2-19	CAGCAGGGACAGTG
538.	TGF-ß2-20	CTTGCTTCTAGTTCTTCAC
539.	TGF-ß2-21	GCCATCAATACCTGC
540.	TGF-ß2-22	GGTGCCATCAATACC
541.	TGF-ß2-23	CCACTGGTATATGTGG
542.	TGF-ß2-24	GGACTTTATAGTTTTCTG
543.	TGF-ß2-25	CTCAAGTCTGTAGGAG
544.	TGF-ß2-26	GGTCTGTTGTGACTC
545.	TGF-ß2-27	CAATTATCCTGCACATTTC
546.	TGF-ß2-28	GCAGCAATTATCCTGC
547.	TGF-ß2-29	GGCAGCAATTATCC
548.	TGF-ß2-30	GGTTCGTGTATCCATTTCC
549.	TGF-ß2-31	GCACAGAAGTTGGC
550.	TGF-ß2-32	CCAGCACAGAAGTTGG
551.	TGF-ß2-33	GTGCTGAGTGTCTG
552.	TGF-ß2-34	CCTGCTGTGCTGAGTG
553.	TGF-ß2-35	GCTCAGGACCCTGC
554.	TGF-ß2-36	GCAGCAAGGAGAAGC
555.	TGF-ß2-37	CCAATGTAGTAGAGAATGG
556.	TGF-ß2-38	GCTGCATTTGCAAG
557.	TGF-ß2-N-1	AAAAAAGAAATCAA
558.	TGF-ß2-N-2	AAAAAAAGAAATCAA
559.	TGF-ß2-N-3	AAAAAAAAGAAATCAA
560.	TGF-ß2-N-4	TAAAAAAAAGAAATCAA
561.	TGF-ß2-N-5	ATAAAAAAAAGAAATCAA
562.	TGF-ß2-N-6	AATAAAAAAAAGAAATCAA
563.	TGF-ß2-N-7	GAATAAAAAAAAGAAAT
564.	TGF-ß2-N-8	AGAATAAAAAAAAGAAAT
565.	TGF-ß2-N-9	CAGAATAAAAAAAA
566.	TGF-ß2-N-10	TCAGAATAAAAAAA
567.	TGF-ß2-N-11	TTGTTTTTAAAAGT
568.	TGF-ß2-N-12	AGTTGTTTTTAAAA
569.	TGF-ß2-N-13	AAGTTGTTTTTAAAA
570.	TGF-ß2-N-14	AAAGTTGTTTTTAAAA
571.	TGF-ß2-N-15	AAAAGTTGTTTTTAAAA
572.	TGF-ß2-N-16	AAAAAGTTGTTTTTAAAA
573.	TGF-ß2-N-17	AAAAAAGTTGTTTTTAAAA
574.	TGF-ß2-N-18	AAAAAAAGTTGTTTTTAAAA
575.	TGF-ß2-N-19	AAAAAAAAGTTGTTTTTAAA
576.	TGF-ß2-N-20	TTTTTAAAAAAAGTG
577.	TGF-ß2-N-21	TTTTTTAAAAAAAGTG
578.	TGF-ß2-N-22	ATTTTTTAAAAAAAGTG
579.	TGF-ß2-N-23	CATTTTTTAAAAAAAGT
580.	TGF-ß2-N-24	GCATTTTTTAAAAAA
581.	TGF-ß2-N-25	TGCATTTTTTAAAAAA
582.	TGF-ß2-N-26	AGCTTATTTTAAAT
583.	TGF-ß2-N-27	AAGCTTATTTTAAAT
584.	TGF-ß2-N-28	TAAGCTTATTTTAAAT
585	TGF-ß2-N-29	TGTAATTATTAGAT

Fig. 3 - 9

586.	TGF-ß2-N-30	ATGTAATTATTAGAT
587.	TGF-ß2-N-31	TGATGTAATTATTA
588.	TGF-ß2-N-32	ATGATGTAATTATTA
589.	TGF-ß2-N-33	ATGGTATTATATAA
590.	TGF-ß2-N-34	TATGGTATTATATAA
591.	TGF-ß2-N-35	TTATGGTATTATATAA
592.	TGF-ß2-N-36	TTTATGGTATTATATAA
593.	TGF-ß2-N-37	ATTTATGGTATTATATAA
594.	TGF-ß2-N-38	AATCATATTAGAAA
595.	TGF-ß2-N-39	TTACAATCATATTA
596.	TGF-ß2-N-40	TTTACAATCATATTA
597.	rb-1	GGCATGACGCCTTTCC
598.	rb-2	GCATGACGCCTTTC
599.	rb-3	GCCTGACGAGAGGC
600.	rb-4	CTCAAGCCTGACGAG
601.	rb-5	CCACAGTTCCTTTTTC
602.	rb-6	GCTGCAATAAAGATACAG
603.	rb-7	GCTGCAATAAAGATAC
604.	rb-8	GGACACTGATTTCTATG
605.	rb-9	GCATTATCAACTTTGG
606.	rb-10	ACTTTTAGCACCAATG
607.	rb-11	CCAAGAAACTTTTAGCACC
608.	rb-12	CCAGATCATCTTCC
609.	rb-13	AGTCAAGGACACATAG
610.	rb-14	TCTTTGAGCAACATGG
611.	rb-15	GGGTATAACAGCTG
612.	rb-16	GAGGTGAACCATTAATGG
613.	rb-17	TCTTCGTATCGTTTAG
614.	rb-18	TGTTGGATAGTGTTC
615.	rb-19	GTTGATCACTTGCTG
616.	rb-20	GGATTCCATTACTCG
617.	rb-21	GACATATGAAAAATGTTGTC
618.	rb-22	GCCAATAAAGACATATG
619.	rb-23	CCAGAATCAAGATTCTG
620.	rb-24	CTGTTCCAGAATCAAG
621.	rb-25	GACAAATCTGTTCCAGAATC
622.	rb-26	GGAAAGACAAATCTGTTCC
623.	rb-27	GATTAAGAGGACAAGC
624.	rb-28	GGAAGATTAAGAGG
625.	rb-29	GCAGTGTGATTATTCTGG
626.	rb-30	GGAGAAAGATACATATCTG
627.	rb-31	GGAGATCTTACAGG
628.	rb-32	GCATTTGCAGTAGAATTTAC
629.	rb-33	CAGTGAAAGAGAGG
630.	rb-34	GCTAGCCGATACAC
631.	rb-35	GGAAGATCCTTGTATGC
632.	rb-36	GCATGAGGAAGATCC
633.	rb-37	GGAGTCATTTTTGTTG
634.	rb-38	CCAATTGATACTAAGATTC
635.	rb-39	TCTTTTGAGCACACG
636.	rb-40	CCTTCAGCACTTCTTTTG
637.	rb-41	GGTTGCTTCCTTCAGC
638.	rb-42	CAGTGGTTTAGGAG
639.	rb-43	CCTGAGATCCTCATTTC
640.	rb-44	CCAAGGTCCTGAGATCC
641.	rb-45	GGTGTACACAGTGTCC
642.	rb-N-1	TATCTTTAATTTCT
643.	rb-N-2	TCTTTTGAATATAA
644.	rb-N-3	TTCTTTTGAATATAA
645.	rb-N-4	TTTCTTTTGAATATAA
646.	rb-N-5	TTTTCTTTTGAATATAA
647.	rb-N-6	TTTTTCTTTTGAATATAA
648.	rb-N-7	ATTTCTATGTTTTT
649.	rb-N-8	TTAAAGAATTTATG
650.	rb-N-9	GTTAAAGAATTTAT

Fig. 3 - 10

651.	rb-N-10	AGTTAAAGAATTTAT
652.	rb-N-11	AAGTTAAAGAATTTAT
653.	rb-N-12	TAAGTTAAAGAATTTAT
654.	rb-N-13	TTTAGTAAGTTAAA
655.	rb-N-14	TTTTAGTAAGTTAAA
656.	rb-N-15	ATTTCTTTTAGTAA
657.	rb-N-16	AATTTCTTTTAGTAA
658.	rb-N-17	ATCAATTTCTTTTA
659.	rb-N-18	TATCAATTTCTTTTA
660.	rb-N-19	AATATATAAGTTCA
661.	rb-N-20	AAATATATAAGTTCA
662.	rb-N-21	CAAATATATAAGTT
663.	rb-N-22	TCAAATATATAAGTT
664.	rb-N-23	TGTCAAATATATAA
665.	rb-N-24	AATTTATTTCAGTA
666.	rb-N-25	AATAAAAATGTGAT
667.	rb-N-26	TAATAAAAATGTGAT
668.	rb-N-27	TAGCTAATAAAAAT
669.	rb-N-28	TTAGCTAATAAAAAT
670.	rb-N-29	TTTAGCTAATAAAAAT
671.	rb-N-30	AATAAAATAGTCAA
672.	rb-N-31	TAATAAAATAGTCAA
673.	rb-N-32	TTAATAAAATAGTCAA
674.	rb-N-33	TTTAATAAAATAGTCAA
675.	rb-N-34	GTTTAATAAAATAGT
676.	rb-N-35	AGTTTAATAAAATAGT
677.	rb-N-36	GAGTTTAATAAAATA
678.	rb-N-37	AGAGTTTAATAAAATA
679.	rb-N-38	AATAATTCTTGTAT
680.	rb-N-39	TATATTACATTCAT
681.	rb-N-40	ATCTATATTACATT
682.	rb-N-41	ATAAACATTTTTCA
683.	rb-N-42	AATAAACATTTTTCA
684.	rb-N-43	AAATAAACATTTTTCA
685.	rb-N-44	GAAATAAACATTTTT
686.	rb-N-45	TGAAATAAACATTTTT
687.	rb-N-46	TTGAAATAAACATTTTT
688.	rb-N-47	TTTGAAATAAACATTTTT
689.	rb-N-48	TTTTGAAATAAACATTTTT
690.	rb-N-49	TTTTTGAAATAAACATTTTT
691.	rb-N-50	ATTTTTGAAATAAACATTTT
692.	rb-N-51	AATTTTTGAAATAAACATT
693.	rb-N-52	AAATTTTTGAAATAAACATT
694.	rb-N-53	AAAATTTTTGAAATAAACAT
695.	rb-N-54	TAAAATTTTTGAAATAAACA
696.	rb-N-55	ATAAAATTTTTGAAATAAAC
697.	rb-N-56	TATAAAATTTTTGAAATAAA
698.	rb-N-57	GTATAAAATTTTTGAAAT
699.	rb-N-58	GGTATAAAATTTTT
700.	rb-N-59	AGGTATAAAATTTTT
701.	rb-N-60	AAGGTATAAAATTTTT
702.	rb-N-61	AAAGGTATAAAATTTTT
703.	rb-N-62	AAAAGGTATAAAATTTTT
704.	rb-N-63	TAAAAGGTATAAAATTTTT
705.	rb-N-64	ATAAAAGGTATAAAATTTTT
706.	rb-N-65	TTTAGAAAGATTTT
707.	rb-N-66	AAGATAAATTTCTT
708.	rb-N-67	TAAGATAAATTTCTT
709.	rb-N-68	TTAAGATAAATTTCTT
710.	rb-N-69	TTTAAGATAAATTTCTT
711.	rb-N-70	TTTTAAGATAAATTTCTT
712.	rb-N-71	TTTTTAAGATAAATTTCTT
713.	rb-N-72	ATTTTTAAGATAAATTTCTT
714.	rb-N-73	TATTTTTAAGATAAATTTCT
715.	rb-N-74	TTATTTTTAAGATAAATT
716.	rb-N-75	TTTATTTTTAAGATAAATT
717.	rb-N-76	CTTTATTTTTAAGATAAAT

Fig. 3 - 11

718.	rb-N-77	TCTTTATTTTTAAGATAAAT
719.	rb-N-78	ATCTTTATTTTTAAGATAAA
720.	rb-N-79	ATCTTTATTTTTAA
721.	rb-N-80	GATCTTTATTTTTAA
722.	rb-N-81	AGATCTTTATTTTTAA
723.	rb-N-82	TAGATCTTTATTTTTAA
724.	rb-N-83	AATCATCATTAATT
725.	rb-N-84	AAATCATCATTAATT
726.	rb-N-85	AAAATCATCATTAATT
727.	rb-N-86	TAAAATCATCATTAATT
728.	rb-N-87	TTAAAATCATCATTAATT
729.	rb-N-88	TTTAAAATCATCATTAATT
730.	rb-N-89	ATTTAAAATCATCATTAATT
731.	rb-N-90	AATTTAAAATCATCATTAA
732.	rb-N-91	GAATTTAAAATCAT
733.	rb-N-92	TGAATTTAAAATCAT
734.	rb-N-93	TTAAAATAGGAAAT
735.	rb-N-94	AATTTCTCTTTAAA
736.	rb-N-95	AAATTTCTCTTTAAA
737.	rb-N-96	TAAAATTTTGAATG
738.	rb-N-97	CTAAAATTTTGAAT
739.	rb-N-98	TTTGCTAAAATTTT
740.	rb-N-99	ATATGAAAAATGTT
741.	rb-N-100	TTTTAAATTAAGCA
742.	rb-N-101	TTGTAAAAATCAAA
743.	rb-N-102	TTTGTAAAAATCAAA
744.	rb-N-103	TTTGATAAAACTTT
745.	rb-N-104	ATGTTTTATCATTT
746.	rb-N-105	AATGTTTTATCATTT
747.	rb-N-106	AAATGTTTTATCATTT
748.	rb-N-107	TAAATGTTTTATCATTT
749.	rb-N-108	TCTAAATGTTTTAT
750.	rb-N-109	TTCTAAATGTTTTAT
751.	rb-N-110	TAAGATCAAATAAA
752.	rb-N-111	ATAAGATCAAATAAA
753.	rb-N-112	AATAAGATCAAATAAA
754.	rb-N-113	TAATAAGATCAAATAAA
755.	rb-N-114	TTAATAAGATCAAATAAA
756.	rb-N-115	TTTAATAAGATCAAATAAA
757.	rb-N-116	TTGTTTAATAAGAT
758.	rb-N-117	ATTGTTTAATAAGAT
759.	rb-N-118	TGATTGTTTAATAA
760.	rb-N-119	TTGATTGTTTAATAA
761.	rb-N-120	TTTGATTGTTTAATAA
762.	rb-N-121	TTTTATAAAACAGT
763.	rb-N-122	TTTTTATAAAACAGT
764.	rb-N-123	TTTTTTATAAAACAGT
765.	rb-N-124	CTTTTTTATAAAACA
766.	rb-N-125	ACTTTTTTATAAAACA
767.	rb-N-126	CACTTTTTTATAAAA
768.	rb-N-127	ACACTTTTTTATAAAA
769.	rb-N-128	TACACTTTTTTATAAAA
770.	rb-N-129	ATACACTTTTTTATAAAA
771.	rb-N-130	ATTTTGAATTTAAG
772.	rb-N-131	GATTTTGAATTTAA
773.	rb-N-132	TGATTTTGAATTTAA
774.	rb-N-133	ATGATTTTGAATTTAA
775.	rb-N-134	AATGATTTTGAATTTAA
776.	rb-N-135	ATAATAGAATCATA
777.	rb-N-136	TATAATAGAATCATA
778.	rb-N-137	TATAATAGAATCAT
779.	rb-N-138	TACTATAATAGAAT
780.	rb-N-139	ATACTATAATAGAAT
781.	rb-N-140	AATACTATAATAGAAT
782.	rb-N-141	AGAATACTATAATA
783.	rb-N-142	TAGAATACTATAATA
784.	rb-N-143	ATAGAATACTATAATA

Fig. 3 - 12

785.	rb-N-144	TATAGAATACTATAATA
786.	rb-N-145	TTATAGAATACTATAATA
787.	rb-N-146	AATATTTGTTTTCA
788.	rb-N-147	AAATATTTGTTTTCA
789.	rb-N-148	AAAATATTTGTTTTCA
790.	rb-N-149	CAAAATATTTGTTTT
791.	rb-N-150	AAATTTTATATGGA
792.	rb-N-151	TGAAATTTTATATG
793.	rb-N-152	CTGAAATTTTATAT
794.	rb-N-153	TCTGAAATTTTATAT
795.	rb-N-154	TTCTGAAATTTTATAT
796.	rb-N-155	ATCTGATTTATTTT
797.	rb-N-156	AAGATATTAAATGT
798.	rb-N-157	TGAAGATATTAAAT
799.	rb-N-158	ATAAATAACAATGA
800.	rb-N-159	TATAAATAACAATGA
801.	rb-N-160	GTATAAATAACAAT
802.	rb-N-161	TGTATAAATAACAAT
803.	rb-N-162	TTGTATAAATAACAAT
804.	rb-N-163	TCTTGTATAAATAA
805.	rb-N-164	ATCTTGTATAAATAA
806.	rb-N-165	AATCTTGTATAAATAA
807.	rb-N-166	ACAACTTTTTAAAT
808.	rb-N-167	TACAACTTTTTAAAT
809.	rb-N-168	TACAACTTTTTAAA
810.	rb-T-1	CGGGGGGTTTTGGGCGGCATG
811.	rb-T-2	TTTTCGGGGGGTTTTGGGCGGCA
812.	rb-T-3	TCGGGGGGTTTTGGGCGGC
813.	rb-T-4	GGTGGCGGCCGTTTTTCGGGGGGT
814.	rb-T-5	CCGGGGGTTCCGCGGCGGCAGCG
815.	rb-T-6	CGGGGGTTCCGCGGCGG
816.	rb-T-7	GGCGGCGGTGCCGGGGGTTCCGC
817.	rb-T-8	GGAGGGGGCGGCGGCGGCGGTG
818.	rb-T-9	GGGGGCGGCGGCGGCGG
819.	rb-T-10	GGGGCGGCGGCGGCG
820.	rb-T-11	AGGGGGCCTGGTGGAAG
821.	rb-T-12	TAGGGGGCCTGGTG
822.	rb-T-13	GTAGGGGGCCTGGT
823.	rb-T-14	GAGGTATTGGTGACAAGGTAGGGGGC
824.	rb-T-15	TCTTCAGGGGTGAAATATAGATGTTC
825.	rb-T-16	GGACTCTTCAGGGGTG

Fig. 3 - 13

826	TCGGACTATA CTGC
827	CAGTTCGGAC TATACT
828	AAGCCTAAGA CGCA
829	GCCCAAGTTC AACA
830	TGAAAAGTCG CGGT
831	GGTTAATTAA GATGCCTC
832	TCTCTAAGAG CGCA
833	ACGTGAGGTT AGTTTG
834	CACGTGAGGT TAGT
835	CATAGAACAG TCCG
836	CAGTCATAGA ACAGTC
837	CTTTGCAGTC ATAGAACA
838	TGCAGTCATA GAAC
839	GGTCGTTTCC ATCT
840	CATAGAAGGT CGTTTC
841	CGTCATAGAA GGTC
842	CATCGTCATA GAAGG
843	GGACGGGAGG AACGAGGCGT TGAG
844	TAGCCATAAG GTCC
845	GGTTACTGTA GCCA
846	GGTTACTGTA GCCA
847	AGTTCTTGGC GCGGAGGT
848	AGGTGAGGAG GTCCGAGT
849	TGGACTGGAT TATCAG
850	GTGGTGGTGA TGTGCCCG
851	TGTCACGTTC TTGG
852	CTCATCTGTC ACGT
853	CGAAGCCCTC GGCGAACC
854	GCGTGTTCTG GCTGTGCAGT TCGG
855	CTGCCCCGTT GACC
856	AGGTTTGCGT AGAC
857	GGTTGAAGTT GCTG
858	CTGGGTTGAA GTTG
859	TGCTGCACGG GCATCTGCTG
860	GGCACTGTCT GAGGCTCCTC CTTCAGG
861	ACTCCATGTC GATG
862	CTCTCCGCCT TGATCC
863	GTTCCTCATG CGCTTC
864	CTGAGCTTTC AAGG
865	GCGATTCTCT CCAGCTTCCT TTTTCG
866	CTGAGCTTTC AAGGTTTTCA CTTTTTCCTC
867	TCCCTGAGCA TGTT
868	TCTGTTTAAG CTGTGC
869	CTTTCTGTTT AAGCTGTG
870	GGTTCATGAC TTTCTG
871	CGTGGTTCAT GACT
872	ACTGTTAACG TGGTTC
873	CCACTGTTAA CGTG
874	CCCACTGTTA ACGT
875	AGCATGAGTT GGCA
876	GCGTTAGCAT GAGT
877	GTTTGCAACT GCTG
878	CAAAATGTTT GCAACTGC

Fig. 4 - 1

879	TCCATTTTAG TGCACATC
880	CTGTTCCATT TTAGTGCA
881	GTGTATGAGT CGTC
882	CTGTGTATGA GTCG
883	CGTAGCTGTG TATG
884	TCGTGTAGAG AGAG
885	AGTTTGTAGT CGTGTAGA
886	GTTTGTAGTC GTGTAG
887	AGTTTGTAGT CGTG
888	GGAGTTTGTA GTCG
889	TCAGGAGTTT GTAGTC
890	GTTTCAGGAG TTTGTAGT
891	TCGGTTTCAG GAGT
892	TTGAGACTCC GGTA
893	ACCAGAAAAG TAGCTG
894	CCTGACCAGA AAAG
895	ATTCAGGCGT TCCA
896	GGTAAAAGTA CTGTCC
897	GGGTAAAAGT ACTGTC
898	GCACCTCCAC CGCTGCCA
899	CTCCTGCTCC TCGGTGAC
900	GCTTTGACAA AGCC
901	CTTGTGCAGA TCGT
902	TCATCTTGTG CAGATC
903	GTTCATCTTG TGCAGA
904	CGTGGTTCAT CTTG
905	TCACGTGGTT CATC
906	GGTTGGTGTA AACG
907	TACGAGCTCC CGGTCCCGAC
908	TAGCTGATGG TGGT
909	TCCTTGAAGG TGGA
910	TCTTCCATGT TGATGG
911	CTTTGATGCG CTCT
912	CTCCACTTTG ATGC
913	GCTCCAGCTT CCGCTTCCGG CACTTGGTGG
914	GGCCTTGAGC GTCTTCACCT TGTCCTCCAG
915	TGACCTTCTG TTTGAG
916	CATGACCTTC TGTTTG
917	GTCATGACCT TCTG
918	CGAGAACATC ATCG
919	GTAGTCTGCG TTGA
920	GCTGCAGCGG GAGGATGACG
921	AGTAAGAGAG GCTATC
922	GTAGTAAGAG AGGC
923	GGTAGTAAGA GAGG
924	GTGAGTGGTA GTAAGA
925	GTCCGTGCAG AAGTCCTG
926	GAATGAAGTT GGCACT
927	GGAATGAAGT TGGC
928	GGGAATGAAG TTGG
929	GCTGCACCAG CCACTGCAGG TCCGGACTGG
930	TCATGGTCTT CACAAC
931	CAATGCTCTG CGCTCGGCCT CCTGTCATGG

Fig. 4 - 2

932	CTAGAGTTCC TCAC
933	GAGTACGCTA GAGT
934	GAAGAGTACG CTAG
935	CTGCTTCCCA CCCAGCCCCC ACATTCCC
936	TTCATCCTCT GTACTGGGCT
937	GTTACGGATG TGCA
938	CAGTTACGGA TGTG
939	CCAGTTACGG ATGT
940	AGAGTCTGAG TTGG
941	GTGAGACTCA GAGT
942	TCTTAGGGTG AGAC
943	GAGAGTACTT CTTAGG
944	GGAAGAAACT ATGAGAGT
945	CTTAGGGAAG AAACTATG
946	CGGTAAGAAA CTTAGG
947	AGCATGCGGT AAGA
948	GTCTGAAAGC ATGC
949	AGAACAAAGA AGAGCC
950	CAAGAGAACA AAGAAGAG
951	CAGCAAGAGA ACAAAG
952	TCCTCAGCAA GAGA
953	AGGTGTGACT TGCA
954	GAATAGGTGT GACTTG
955	CAGAATAGGT GTGACT
956	GCAGAATAGG TGTG
957	CAGTTGCAGA ATAGGT
958	GAAACCATTT CTGACC
959	TGTGAAACCA TTTCTGAC
960	CACTGTGAAA CCATTTCT
961	CCACTGTGAA ACCA
962	AGAACTGGCT CCTGCAGCTT CCCTGCTTCC
963	CACCTCCATT CACCC
964	CAGTAAAAGT GTCTGC
965	CGACATTCAG TAAAAGTG
966	GACCGACATT CAGT
967	CTTCTGGAGA TAACTAGA
968	CATCTTATTC CTTTCCCT
969	CAGCCATCTT ATTCCT
970	TGCAGCCATC TTATTC
971	GAGTGTATCA GTCAG
972	GGAGTGTATC AGTC
973	CTTGGAGTGT ATCAGT
974	ACAGAGTACC TACC
975	CCAACTTTCC CTTAAG
976	CCTTATGCTC AATCTC
977	GTCTTACTCA AGGG
978	ACAGTCTTAC TCAAGG
979	CATAAGACAC AGTCTTAC
980	GAAAGCATAA GACACAGT
981	GGAAAGCATA AGACAC
982	AGGGATAAAG GAAAGC
983	CCTGTATACA GAGG
984	TGTCTCCTGT ATACAG

Fig. 4 - 3

985	CATCTTCTAG TTGGTC
986	CTCATCTTCT AGTTGG
987	CTTCTCATCT TCTAGTTG
988	CAAAGCAGAC TTCTCA
989	CTGCAAAGCA GACT
990	CTAGTTTTTC CTTCTCCT
991	TCTAGTTTTT CCTTCTCC
992	CAGGATGAAC TCTAGT
993	TCGTAGAAGG TCGT
994	AGGGTTACTG TAGC
995	GTAGTGGTGA TGTG
996	CGTCGTAGAA GGTC
997	TTTCGTGCAC ATCC
998	AGTTTGTAGT CGTGAAGA
999	CGAGAACATC ATGG
1000	GTAGTAGGAA AGGC
1001	GGTAGTAGGA AAGG
1002	GGAATGGTAG TAGG
1003	GGTCATTGAG AAGAG
1004	GCTAATGTTC TTGACC
1005	GCCAAGGTCCTCAT
1006	GGAGTCTATCTCCA
1007	CCAAAGAATCCTGACT
1008	CACATGCTTAGTGG
1009	CTCGTAAATGACCG
1010	AGGAATCTCGTAAATGAC
1011	CAGCAGCGATTCAT
1012	GGAGATCATCAAAGGA
1013	CTCAGCAATGGTCA
1014	GATCTCGAACACCT
1015	CACAATCTCGATCTTTCT
1016	CCTTCTTAAAGATTGGCT
1017	CACATACCAACTGG
1018	AGCTTGATGTGAGG
1019	GAAGTTGTAGCTTGATGT
1020	GCTTGAAGTTGTAGCT
1021	CTGCTTGAAGTTGTAG
1022	GACACAACTCCTCT
1023	TCCTTTGATAGACACAAC
1024	CTCGTTTGATAGACAC
1025	GGTTAGCACACACT
1026	GGTAACGGTTAGCA
1027	CGTAACACATTTAGAAGC
1028	CTCATCCGTAACAC
1029	CCGGTAAGTATTGTAGTT
1030	GGTGTATTTCCTTGAC
1031	ACATACCAACTGGTGT
1032	GTCCCTATACGAAC
1033	TTCATGTCTG TGCC
1034	GTAGGTGAGT TCCA
1035	GTTGTGAGCG ATGA
1036	CATAGTTGTC CTCAAAGA
1037	GGCATAGTTG TCCT

Fig. 4 - 4

1038	CATTGTCTAG CACG
1039	CTCCATTGTC TAGC
1040	GTATTGTTCA GCGG
1041	TCAAGATCTC TGTGAG
1042	CACAAAATCG TGTCCT
1043	TCCTTCCACA AAATCG
1044	GTGGAAGATG TCCT
1045	TCTTGTGGAA GATGTC
1046	TCTATCAGTG TGAGAG
1047	GGTTGGTGTC TATC
1048	ACATCGGAGA ACAG
1049	CCTTACACAT CGGA
1050	ACAATCCTCA GAACTC
1051	GCTCTGACAA TCCT
1052	TGGTTGAAGT GGAG
1053	CTGTGGTTGA AGTG
1054	GTTGTAGGTG ACCA
1055	CTGTGTTGTA GGTG
1056	GACTCAAACG TGTC
1057	CATGGACTCA AACG
1058	CGAATGTATA CCGG
1059	CCGAATGTAT ACCG
1060	GCCGAATGTA TACC
1061	GTAGTTGTAG GGAC
1062	TAGAAAGGTA GTTGTAGG
1063	GTAGAAAGGT AGTTGTAG
1064	CGTAGAAAGG TAGTTG
1065	CCGTAGAAAG GTAG
1066	GACCATAGCA CACT
1067	GGATATTGGC ACTG
1068	CCTGGATATT GGCA
1069	GCTCCCAAAG ATCT
1070	CCCATCAAAG CTCT
1071	CAAACACTTG GAGC
1072	GTCTCAAACA CTTGGA
1073	GAGTCTCAAA CACTTG
1074	GTAACCTGTG ATCTCT
1075	GGTAACCTGT GATC
1076	GTATAGGTAA CCTGTG
1077	TGAGATGTAT AGGTAACC
1078	TGCTGAGATG TATAGG
1079	CCATGCTGAG ATGT
1080	GGATTACTTG CAGG
1081	TGTTATGGTG GATGAG
1082	GGTGTTATGG TGGA
1083	GCAGTTGACA CACT
1084	AGTACTCGGC ATTC
1085	CATTCACATA CTCCCT
1086	TCCAAAACAG GTCACT
1087	GGTCCTTATA GTGG
1088	CAGAATGCCA ACCA
1089	ACGAGAATGC CAAC
1090	GATCCCAAAG ACCA

Fig. 4 - 5

1091	TCGCTTGATG AGGA
1092	CATCGTGTAC TTCC
1093	GCATCGTGTA CTTC
1094	ACTGTGCCAA AAGC
1095	CTTGTAGACT GTGC
1096	CCCTTGTAGA CTGT
1097	TCAACACTTT GATGGC
1098	CCCTCAACAC TTTG
1099	GTGTTTTCCC TCAACA
1100	GTATGCTTCG TCTAAG
1101	CGTATGCTTC GTCT
1102	CCATCACGTA TGCT
1103	GCATAAGCTG TGTC
1104	CATGGTCTAA GAGG
1105	CAATCTGCAT ACACCA
1106	GGCAATCTGC ATAC
1107	CTGTCTCGTC AATG
1108	CATAACTCCA CACATC
1109	AGTCACACCA TAACTC
1110	ACAGTCACAC CATAAC
1111	CCCCAAAAGT CATC
1112	TCGTAAGGTT TGGC
1113	GATCCCATCG TAAG
1114	CAATGGTGCA GATG
1115	GACATCAATG GTGC
1116	GTAGACATCA ATGGTG
1117	CATGATCATG TAGACATC
1118	CCATGATCAT GTAGAC
1119	CATTTGACCA TGATCATG
1120	CCAACATTTG ACCATG
1121	TCATCCAACA TTTGACCA
1122	GAGTCAATCA TCCAACAT
1123	CAGAGTCAAT CATCCA
1124	CCGACATTCA GAGT
1125	GAATTCAGAC ACCAAC
1126	GATGACCACA AAGC
1127	CCATCAAATA CATCGG
1128	TCACCATCAA ATACATCG
1129	CAACGTAGCC ATCA
1130	ACGTCTTTGA CGAC
1131	CAAAAACGTC TTTGACGA
1132	GGCAAAAACG TCTTTG
1133	CAAAGGCAAA AACGTC
1134	GTGTCAAGTA CTCG
1135	GTAATAGAGG TTGTCG
1136	CCCAGTAATA GAGG
1137	CATGGTGCTC ACTG
1138	GTGCCTGTAC GTAC
1139	TGCAGGTGGA TAGT
1140	CATGTCGATA GTCTTGCA
1141	GTCGATAGTC TTGC
1142	CCATGTCGAT AGTC
1143	CTCCATGTCG ATAG

Fig. 4 - 6

1144	CTTGGACAGG ATCT
1145	TGCTGTTGTA CAGG
1146	GTGCTGTTGT ACAG
1147	TTGGCGTAGT AGTC
1148	TCCACCATTA GCAC
1149	GATTTCGTTG TGGG
1150	GTCATAGATT TCGTTGTG
1151	TGTACTCTGC TTGAAC
1152	GTGTACTCTG CTTG
1153	TGCTGTGTGT ACTC
1154	CTGATGTGTT GAAGAACA
1155	CTCTGATGTG TTGAAG
1156	GCTCTGATGT GTTG
1157	GAGCTCTGAT GTGT
1158	CACTTTTAAC TTGAGCCT
1159	CTCCACTTTT AACTTGAG
1160	TGCTGTATTT CTGGTACA
1161	CCAGGAATTG TTGC
1162	TTGCTGAGGT ATCG
1163	GATAACCACT CTGG
1164	CAAAAGATAA CCACTCTG
1165	CGGTGACATC AAAAG
1166	CCTCAATTTC CCCT
1167	GTTATCCCTG CTGT
1168	GCAGTGTGTT ATCC
1169	GATGTCCACT TGCA
1170	TAGTGAACCC GTTG
1171	TGCCATGAAT GGTG
1172	GTTCATGCCA TGAATG
1173	CATGAGAAGC AGGA
1174	GCTTTGCAGA TGCT
1175	GAGCTTTGCA GATG
1176	TAGTTGGTGT CCAG
1177	CTGAAGCAAT AGTTGG
1178	AGCTGAAGCA ATAGTTGG
1179	GGAGCTGAAG CAAT
1180	CAATGTACAG CTGC
1181	GGAAGTCAAT GTACAG
1182	CGGAAGTCAA TGTAC
1183	GCGGAAGTCA ATGT
1184	AGTTGGCATG GTAG
1185	GCAGAAGTTG GCAT
1186	CTCCAAATGT AGGG
1187	ACCTTGCTGT ACTG
1188	TGCTGGTTGT ACAG
1189	GGTTATGCTG GTTG
1190	GTAGTACACG ATGG
1191	CGTAGTACAC GATG
1192	CACGTAGTAC ACGA
1193	CATGTTGGAC AGCT
1194	GCACGATCAT GTTG
1195	CACACAGTAG TGCA
1196	GATCAGAAAA GCGC

Fig. 4 - 7

1197	ACCGTGACCA GATG
1198	GTAGACAGGC TGAG
1199	TATCGAGTGT GCTG
1200	TTGCGCATGA ACTG
1201	TTGCTCAGGA TCTG
1202	ACTGGTGAGC TTCA
1203	GCTCAGGATA GTCT
1204	TGTAGATGGA AATCACCT
1205	TGGTGCTGTT GTAG
1206	TTCTCCTGGA GCAA
1207	TACTCTTCGT CGCT
1208	CTTGGCGTAG TACT
1209	CGGCATGTCT ATTTTGTA
1210	CGGGATGGCA TTTT
1211	CTGTAGAAAG TGGG
1212	ACAATTCTGA AGTAGGGT
1213	ATTGCTGAGA CGTCAAAT
1214	TCTCCATTGC TGAG
1215	TCACCAAATT GGAAGCAT
1216	CTCTGAACTC TGCT
1217	AACGAAAGAC TCTGAACT
1218	TGGGTTCTGC AAAC
1219	CTGGCTTTTG GGTT
1220	GTTGTTCAGG CACT
1221	TCTGATATAG CTCAATCC
1222	TCTTTGGACT TGAGAATC
1223	TGGGTTGGAG ATGT
1224	TGCTGTCGAT GTAG
1225	ACAACTTTGC TGTCGA
1226	ATTCGCCTTC TGCT
1227	GAAGGAGAGC CATT
1228	TCAGTTACAT CGAAGG
1229	TGAAGCCATT CATGAACA
1230	TCCTGTCTTT ATGGTG
1231	AAATCCCAGG TTCC
1232	GGACAGTGTA AGCTTATT
1233	GTACAAAAGT GCAGCA
1234	TAGATGGTAC AAAAGTGC
1235	CACTTTTATT TGGGATGATG
1236	GCAAATCTTG CTTCTAGT
1237	GTGCCATCAA TACC
1238	GGTATATGTG GAGG
1239	TCTGATCACC ACTG
1240	TCCTAGTGGA CTTTATAG
1241	TTTTTCCTAG TGGACT
1242	CAATAACATT AGCAGG
1243	AAGTCTGTAG GAGG
1244	TCTGTTGTGA CTCAAG
1245	GTTGGTCTGT TGTG
1246	CAAAGCACGC TTCT
1247	TTTCTAAAGC AATAGGCC
1248	GCAATTATCC TGCACA
1249	ACGTAGGCAG CAAT

Fig. 4 - 8

1250	ATCAATGTAA AGTGGACG
1251	CTAGATCCCT CTTG
1252	CCATTTCCAC CCTA
1253	TGGGTTCGTG TATC
1254	TGGCATTGTA CCCT
1255	TCCAGCACAG AAGT
1256	ATAAATACGG GCATGC
1257	AGTGTCTGAA CTCC
1258	TGTGCTGAGT GTCT
1259	ATAAGCTCAG GACC
1260	AGGAGAAGCA GATG
1261	AGCAAGGAGA AGCA
1262	AATCTTGGGA CACG
1263	TAGAGAATGG TTAGAGGT
1264	GTTTTGCCAA TGTAGTAG
1265	CTTGGGTGTT TTGC
1266	GCAAGACTTT ACAATC
1267	GCATTTGCAA GACTTTAC
1268	TTTAGCTGCA TTTGCAAG
1269	GCCACTTTTC CAAG
1270	TTGGTCTTGC CACT
1271	CAGCACACAG TAGT
1272	CGATAGTCTT GCAG

Fig. 4 - 9

1273	TGF-ß2-14/1	CTTTCACCAAATTGGAAG
1274	TGF-ß2-14/2	CACCAAATTGGAAGC
1275	TGF-ß2-14/3	TCACCAAATTGGAAGC
1276	TGF-ß2-15/1	CTCTGGCTTTTGGG
1277	TGF-ß2-9/1	CGGCATGTCTATTTTG
1278	relA-1	CACTACAGACGAGC
1279	relA-2	CGTGCACTACAGACG
1280	relA-3	GGAACAGTTCGTCC
1281	relA-4	GAACAGTTCGTCCATG
1282	relA-5	CCAGAGTTTCGGTTC
1283	relA-6	CTAGGACTGGGACAG
1284	relA-7	CGCACTTGTAGCG
1285	relA-8	CTCGCACTTGTAGC
1286	relA-9	GCACTTGTAGC
1287	relA-10	GCGCACTGTCCCTG
1288	relA-11	CCAGGGAGATGCGC
1289	relA-12	GCCGGTGAGGAGG
1290	relA-13	CCGGTGAGGAGGG
1291	relA-14	CGGTTCACTCGGC
1292	relA-15	GAGTTTCGGTTCACTC
1293	relA-16	GGCACGATTGTCAAAG
1294	relA-17	CAGGCGTCACCCCC
1295	relA-18	GCAGGCGTCACCC
1296	p105/p50-1	CTCCCTCCTAAGC
1297	p105/p50-2	CCCTCCTAAGCGG
1298	p105/p50-3	CGAGTCCGCGTTCG
1299	p105/p50-4	CATCTTCTGCCATTC
1300	p105/p50-5	GTGTTTTCCCACCAG
1301	p105/p50-6	GGTTTTGGTTCACTAG
1302	p105/p50-7	GCATCTTCACGTCTCC
1303	p105/p50-8	CTTCACGTCTCCTGTC
1304	p105/p50-9	GTCACCGCGTAGTC
1305	p105/p50-10	CAAATAGGCAAGGTC
1306	p105/p50-11	CTTGCAAATAGGCAAG
1307	p105/p50-12	TGCTTGCAAATAGG
1308	p105/p50-13	CTGCTTGCAAATAGG
1309	p105/p50-14	GCAGGTGGATATTT
1310	p105/p50-15	CTGCTGTTGGCAG
1311	p105/p50-16	CACTAGTTTCCAAGT
1312	p105/p50-17	GTTTTGGTTCACTAG
1313	p105/p50-18	CTTTGATTTCAGGATAG

Fig. 5 – 1

1314	p105/p50-19	GCACTTCTTCTTTATCT
1315	p105/p50-20	CCAAGTCAGATTTCC
1316	p105/p50-21	GTTTCCAAGTCAGATTTC
1317	p105/p50-22	GGTTCACTAGTTTCC
1318	p105/p50-23	GGTTTTGGTTCACTAG
1319	p105/p50-24	CCGAAAAATTGGGCA
1320	p105/p50-25	CCGAAAAATTGGG
1321	p105/p50-26	CTATCCGAAAAATTGG
1322	p105/p50-27	GTTGATAATGTCATCAG
1323	p105/p50-28	CTCATGTTGATAATGTC
1324	p105/p50-29	CTGTCACCGCGTAG
1325	p105/p50-30	CGTCTCCTGTCACCG
1326	p105/p50-31	CTTCACGTCTCCTG
1327	p105/p50-32	GAGAACTTTATCATGTC
1328	p105/p50-33	GCTATATGCAGGG
1329	p105/p50-34	CCAGCTGCTATATGCAGG
1330	p105/p50-35	AGGCTAAATTTTGCCT
1331	p105/p50-36	GGCTAAATTTTGCC
1332	p105/p50-37	GGCTAAATTTTGCCTTC
1333	p105/p50-38	GCAGGCTAAATTTTGCC
1334	p105/p50-39	GAGTTACCCAAGCG
1335	p105/p50-40	CAGAGTTACCCAAGCG
1336	p105/p50-41	CAGAGTTACCCAAG
1337	p105/p50-42	ACAGAGTTACCCAAG
1338	p105/p50-43	GGTGCAAAACAGAG
1339	p105/p50-44	CTAGGTGCAAAACAG
1340	p105/p50-45	GAGAACTTTATCATGTCC
1341	p105/p50-46	GCTAGATGAATGGC
1342	p105/p50-47	GCAAACATGGCAGGC
1343	p105/p50-48	CAGCAAACATGGCA
1344	p105/p50-49	GCAGCAAACATGGC
1345	p105/p50-50	AGCAGCAAACATGG
1346	p105/p50-51	CAGCAGCAAACATG
1347	p105/p50-52	AGCAGCAGCAAACA
1348	p105/p50-53	CAGCAGCAGCAAACA
1349	p105/p50-54	CAGCAGCAGCAAAC
1350	p105/p50-55	CACCAGCAGCAGCA
1351	p105/p50-56	GCATTGACGTCAGC
1352	p105/p50-57	GATGTTGTCGTGCTC
1353	p105/p50-58	TGAGATGTTGTCGTGCT
1354	p105/p50-59	TGAGATGTTGTCGTG

Fig. 5 - 2

1355	p105/p50-60	GCCAATGAGATGTTG
1356	p105/p50-61	CTGCCAATGAGATG
1357	p105/p50-62	CACATGGGCATCAC
1358	p105/p50-63	TGTCCACATGGGCA
1359	p105/p50-64	GTACTGTCCACATG
1360	p105/p50-65	CAGCTGCTATATGC
1361	p105/p50-66	GTTCTCCACCAGGG
1362	p105/p50-67	AGTTCTCCACCAGG
1363	p105/p50-68	CAAAGTTCTCCACCAG
1364	p105/p50-69	CCAAGAGTCATCCAGG
1365	p105/p50-70	CCCAAGAGTCATCC
1366	p105/p50-71	CCTGCATTTTCCCAAG
1367	p105/p50-72	TCCTGCATTTTCCC
1368	p105/p50-73	GCCATATCTAGAGGC
1369	p105/p50-74	TCACATCTTCAGCC
1370	p105/p50-75	GCTTCACATCTTCAGC
1371	p105/p50-76	CAGCTTCACATCTTC
1372	p105/p50-77	GTAACTTATACAGCTGC
1373	p105/p50-78	CCAGTTTTGTCTGG
1374	p105/p50-79	CCATTTGTCTCAGG
1375	p105/p50-80	GTGTAGCCCATTTG
1376	p105/p50-81	GCTTCGGTGTAGCC
1377	p105/p50-82	GATCACTTCAATTGCTTC
1378	p105/p50-83	CTTGTGGAGGCAGG
1379	p105/p50-84	GCTGCCTTGTGGAG
1380	p105/p50-85	CTATTTGCTGCCTTGTGG
1381	p105/p50-86	GGATGTCTCCACGC
1382	p105/p50-87	GGAAGGATGTCTCC
1383	p105/p50-88	TGCGGAAGGATGTC
1384	p105/p50-89	GTTTGCGGAAGGATGTC
1385	p105/p50-90	GCTGAGTTTGCGGA
1386	p105/p50-91	GGTAAAGCTGAGTTTG
1387	p105/p50-92	TCGGTAAAGCTGAG
1388	p105/p50-93	GACTCGGTAAAGCTG
1389	p105/p50-94	AGAGACTCGGTAAAGC
1390	p105/p50-95	GAAATTGTCAGCAGGC
1391	p105/p50-96	GAAATTGTCAGCAGG
1392	p105/p50-97	GGAAATTGTCAGCAGG
1393	p105/p50-98	GGAAATTGTCAGCAG
1394	p105/p50-99	GGGAAATTGTCAGC
1395	p105/p50-100	GTGTGGGAAATTGTC

Fig. 5 – 3

1396	p105/p50-101	GGTTTACACGGTGTG
1397	p105/p50-102	GCTTTGGTTTACACG
1398	p105/p50-103	GCACCTTTGGGATGC
1399	NFKB2-1	CCAGGTTCTGCTTCC
1400	NFKB2-2	GCTCTGTCTAGTGGC
1401	NFKB2-3	ACTCTCCATGTCTC
1402	NFKB2-4	CAACTCTCCATGTCTC
1403	NFKB2-5	CAACTCTCCATGTC
1404	NFKB2-6	AGCAACTCTCCATG
1405	NFKB2-7	GTAGCAACTCTCCATG
1406	NFKB2-8	GTAGCAACTCTCCA
1407	NFKB2-9	GGTTGTAGCAACTCTCC
1408	NFKB2-10	CGGGCAGTCCTCCA
1409	NFKB2-11	GCACCGGGCAGTC
1410	NFKB2-12	AGGCACCGGGCAG
1411	NFKB2-13	GTGTGTTACCAGGTC
1412	NFKB2-14	TGTGTGTTACCAGGT
1413	NFKB2-15	TGGGTCACTGTGTG
1414	NFKB2-16	CAGACTGTGGGCATG
1415	NFKB2-17	CCCACCAGACTGTGGG
1416	NFKB2-18	CCACCAGACTGTGG
1417	NFKB2-19	TGCCCACCAGACTG
1418	NFKB2-20	CGGCTTCCTCCCC
1419	NFKB2-21	CCTTGTCTTCCACC
1420	NFKB2-22	ACCGAGGCTGCCAC
1421	NFKB2-23	GGAAGAAACCGAGG
1422	NFKB2-24	GGGAAGAAACCGAG
1423	NFKB2-25	GGCCATCTGCGCC
1424	NFKB2-26	GCGGCCATCTGCG
1425	NFKB2-27	GTGGCGGCCATCTG
1426	NFKB2-28	ACCGTGGCGGCCAT
1427	NFKB2-29	GCCGCTCAATCTTCATC
1428	NFKB2-30	CTTCATCTTGTGATAGG
1429	NFKB2-31	GCTCAATCTTCATCTTG
1430	NFKB2-32	CAGAAACACTGTTACAG
1431	NFKB2-33	CAGTTGCAGAAACACTG
1432	NFKB2-34	GTTTCAGTTGCAGAAAC
1433	NFKB2-35	CTTCCACCAGAGGG
1434	NFKB2-36	GTCTTCCACCAGAG
1435	NFKB2-37	CTTGTCTTCCACCAGAG
1436	NFKB2-38	TCCTTGTCTTCCAC

Fig. 5 - 4

1437	NFKB2-39	CTTCCTTGTCTTCCAC
1438	NFKB2-40	CATCTTGTGATAGGG
1439	NFKB2-41	GCTAGGTGCAGTGGT
1440	NFKB2-42	GATGGCTAGGTGCA
1441	NFKB2-43	GTGGATGATGGCTAG
1442	NFKB2-44	CCCGTGGATGATGG
1443	NFKB2-45	CTGCCCGTGGATGA
1444	NFKB2-46	AGAGCCTCCACCCA
1445	NFKB2-47	GTTGTACTCTCGAGC
1446	NFKB2-48	CGTTGTACTCTCG
1447	NFKB2-49	CGCGTTGTACTCTC
1448	NFKB2-50	GAGTCTCCATGCCG
1449	NFKB2-51	CTGAGTCTCCATGC
1450	NFKB2-52	CATGGCTGAGTCTC
1451	NFKB2-53	TGCATGGCTGAGTC
1452	NFKB2-54	GCGTTCACGTTGGC
1453	NFKB2-55	GTGCGAGCGTTCAC
1454	NFKB2-56	AGGTGCGAGCGTTC
1455	NFKB2-57	GCAAAGGTGCGAGC
1456	NFKB2-58	CCTGGTGGCTCAGG
1457	NFKB2-59	GTCAGTCACCTGAG
1458	NFKB2-60	CAGGTCAGTCACCTG
1459	NFKB2-61	CAGCAGGTCAGTCAC
1460	NFKB2-62	GCAGCAGGTCAGTC
1461	NFKB2-63	CATTTAGCAGCAAGGTC
1462	NFKB2-64	GCAGCATTTAGCAGC
1463	NFKB2-65	CTGAGCAGCATTTAG
1464	NFKB2-66	CCCATGAGAATCCT
1465	NFKB2-67	CCTTCCCATGAGAATCC
1466	NFKB2-68	TCCTCCCCTTCCCA
1467	NFKB2-69	GCCTCCAGTAGACC
1468	NFKB2-70	GTCAGACAGGGCCT
1469	NFKB2-71	CCATGTCAGACAGG
1470	NFKB2-72	GGCCCATGTCAGAC
1471	TANK-1	GCTATTCCTGAAATCAC
1472	TANK-2	CCTCTTGTCTTCTTACC
1473	TANK-3	GGAGAAGAAACCTCTTG
1474	TANK-4	CCTTGCTGAAGTTTCTT
1475	TANK-5	CCAAGACTCCTTGC
1476	TANK-6	CCCTTTCATGGAGC
1477	TANK-7	CCTCTTGGTGTGAC

Fig. 5 - 5

1478	TANK-8	GACTAAGGATGCCG
1479	TANK-9	GTGGCAGGACTAAGG
1480	TANK-10	AGACGTGGCAGGAC
1481	I-kappa-Bepsilon-1	CTTCCAGCAGGCAG
1482	I-kappa-Bepsilon-2	GTTCCTCTGCCTGG
1483	I-kappa-Bepsilon-3	GATGTTCCTCTGCCTG
1484	I-kappa-Bepsilon-4	GAGATGTTCCTCTGCC
1485	I-kappa-Bepsilon-5	GTGAGATGTTCCTCTG
1486	I-kappa-Bepsilon-6	CAGAGAGTGAGATGTTCC
1487	I-kappa-Bepsilon-7	CCAGAGAGTGAGATGTTC
1488	I-kappa-Bepsilon-8	GGTCCAGAGAGTGAG
1489	I-kappa-Bepsilon-9	GAGGTCCAGAGAGTG
1490	I-kappa-Bepsilon-10	GGTCCTGTAGTGCC
1491	TRAF-6-1	GATTTTATGATGCAGGC
1492	TRAF-6-2	GACCTGCATCCCTTATTG
1493	TRAF-6-3	TAGTTGATTTTCCAGCAG
1494	TRAF-6-4	GAATCTCACGTTTTGC
1495	TRAF-6-5	CAGAGAAAGAATCTCACG
1496	TRAF-6-6	TTTCACCATCAGAGAAAG
1497	TRAF-6-7	CATTTGGACATTTCACC
1498	TRAF-6-8	CCTTCATTTGGACATTTC
1499	TRAF-6-9	CAATGTGCTTGATGATCC
1500	Rank-1	CGCATCGGATTTCTC
1501	Rank-2	CAAACCGCATCGGATTTC
1502	Rank-3	GAACTGCAAACCGC
1503	Rank-4	GCAGAGAAGAACTGC
1504	Rank-5	GCAAGTAAACATGGG
1505	Rank-6	GGTCCACGTTTTGG
1506	Rank-7	GCAAGGGTCCACGTTT
1507	Rank-8	TGGCTTCTTCTTCAGGG
1508	Rank-9	TCCTGCTGGCTTCTTC
1509	Rank-10	GTCCTGCTGGCTTC
1510	IL-5-1	GGTAGTCTAGGAATTGG
1511	IL-5-2	CTTGCAGGTAGTCTAGG
1512	IL-5-3	GAAACTCTTGCAGGTAG
1513	IL-5-4	CACCAAGAAACTCTTGC
1514	IL-5-5	CATTACACCAAGAAACTC
1515	IL-5-6	CTCGGTGTTCATTACACC
1516	IL-5-7	CTTTCTATTATCCACTCG
1517	IL-5-8	CCAGTTTAGTCTCAACTT
1518	IL-5-9	AACCAGTTTAGTCTCAAC

Fig. 5 – 6

1519	IL-5-10	ACAAACCAGTTTAGTCTC
1520	IL-13-1	CTCGCGAAAAAGTTTCTT
1521	IL-13-2	CCCTCGCGAAAAAGTTTC
1522	IL-13-3	GTCCCTCGCGAAAAAG
1523	IL-13-4	CAGTTGAACCGTCCC
1524	IL-13-5	GCTTTCGAAGTTTCAGTT
1525	IL-13-6	GATGCTTTCGAAGTTTC
1526	IL-13-7	CTGTCTCTGCAAATAATG
1527	IL-15-1	CACTTATTACATTCACCC
1528	IL-15-2	TTTTCCTCCAGTTCCTC
1529	IL-15-3	GGACAATATGTACAAAACTC
1530	IL-15-4	GTTGATGAACATTTGGAC
1531	IL-15-5	GTGTTGATGAACATTTGG
1532	I-kappaB(newmember)-1	CAAAATTTGGCCAGGG
1533	I-kappaB(newmember)-2	GCCCAAAATTTGGCC
1534	I-kappaB(newmember)-3	CCCAGCCCAAAATTTGG
1535	I-kappaB(newmember)-4	GTCCCCAGCCCAAAATT
1536	I-kappaB(newmember)-5	AAATCGCCAGAGGCTG
1537	I-kappaB(newmember)-6	ACCAAATCGCCAGAGG
1538	I-kappaB(newmember)-7	CATCACCAAATCGCCAG
1539	Prostaglan.Rec.EP3-1	TAGGAGTGGTTGAGGC
1540	Prostaglan.Rec.EP3-2	GTGTAGGAGTGGTTGAG
1541	Prostaglan.Rec.EP3-3	CTGTGTAGGAGTGG
1542	Prostaglan.Rec.EP3-4	CCCACATGCCTGTG
1543	Prostaglan.Rec.EP3-5	CGATGAACAACGAG
1544	Prostaglan.Rec.EP3-6	CTGGCGATGAACAACG
1545	Prostaglan.Rec.EP3-7	CGCTGGCGATGAAC
1546	Prostaglan.Rec.EP3-8	GAGCTAGTCCCGTTG
1547	Prostaglan.Rec.EP3-9	GCGAAGAGCTAGTCC
1548	Prostaglan.Rec.EP3-10	CCAGTTATGCGAAGAGC
1549	Prostaglan.Rec.EP3-11	CCCCAGTTATGCGAAG
1550	PresenilinI-1	CACATGCTTGGCGC
1551	PresenilinI-2	GATCACATGCTTGGCG
1552	PresenilinI-3	GACAAAGAGCATGATCAC
1553	PresenilinI-4	GAGTCACAGGGACAAAG
1554	PresenilinI-5	GAGAGTCACAGGGAC
1555	PresenilinI-6	GCAGAGAGTCACAGG
1556	PresenilinI-7	CCATGCAGAGAGTC
1557	PresenilinI-8	CCACCATGCAGAGAG
1558	PresenilinI-9	TAGCCACGACCACC
1559	PresenilinI-10	GATTAGCTGCCCATCCTT

Fig. 5 – 7

1560	PresenilinI-11	GGTATAGATTAGCTGCC
1561	PresenilinI-12	GTATCTTCTGTGAATGGG
1562	PresenilinI-13	CTGGCCCACAGTCT
1563	PresenilinI-14	CTCTGGCCCACAGT
1564	PresenilinI-15	TGCAGGGCTCTCTG
1565	PresenilinI-16	AGTGCAGGGCTCTC
1566	PresenilinI-17	CACTGATCATGATGGC
1567	PresenilinI-18	GACACTGATCATGATGGC
1568	PresenilinI-19	ACAATGACACTGATCATG
1569	PresenilinI-20	GAACCACCAGGAGGAT
1570	PresenilinI-21	GACACAAAACAGCCACT
1571	PresenilinI-22	GTGGACCTTTCGGAC
1572	PresenilinI-23	CAACCAGCATACGAAGT
1573	PresenilinI-24	TCCCTCTGGGCTTC
1574	PresenilinI-25	ACTGTCCCTCTGGG
1575	PresenilinI-26	GACTGTCCCTCTGG
1576	PresenilinI-27	CCTAGATGACTGTCCC
1577	PresenilinI-28	CAGCGAGGATACTGC
1578	PresenilinI-29	CTTCACCAGCGAGGAT
1579	PresenilinI-30	TTTCCTCTGGGTCTTCAC
1580	PresenilinI-31	CTTTCCTCTGGGTCTTC
1581	PresenilinI-32	CTCCCAATCCAAGTTTT
1582	TRADD-1	TTCATCCCGGAGCC
1583	TRADD-2	TTCTTCATCCCGGAGC
1584	TRADD-3	GCTCAGCCAGTTCTTC
1585	TRADD-4	GACAGAGAGGGCAC
1586	TRADD-5	CTTCACCTCCGACAG
1587	TRADD-6	GAAAAGTCTGGGCAGG
1588	TRADD-7	GACCCTGGAACAGAAAAG
1589	TRADD-8	CTGACCCTGGAACAG
1590	TRADD-9	ACTACAGGCTGACCCT
1591	TRADD-10	ATTCACTACAGGCTGACC
1592	TRADD-11	CGATTCACTACAGG
1593	TRADD-12	GGCCGATTCACTAC
1594	TRADD-13	CGAACGTCTGTTGGTC
1595	TRADD-14	CGCGAACGTCTGTTG
1596	PKA-1	CTTCTGTTTGTCGAGGAT
1597	PKA-2	TTCACCACCTTCTGTTTG
1598	PKA-3	AGGATGCGCTTTTCATTC
1599	PKA-4	AGCTTGCAGGATGCG
1600	PKA-5	GTTGACAGCTTGCAGGAT

Fig. 5 - 8

1601	PKA-6	GGAACGGAAAGTTGACAG
1602	PKA-7	AACTCGAGTTTGACGAGG
1603	PKA-8	TGTCCTTGAAGGAGAAC
1604	PKA-9	CGTACTCCATGACCATGT
1605	PKA-10	GCACGTACTCCATGAC
1606	PKA-11	GATTCTCCGGCTTCAG
1607	PKA-12	TCAATGAGCAGATTCTCC
1608	PKA-13	GGTCAATGAGCAGATTC
1609	PKA-14	CCCTGCTGGTCAATG
1610	PKA-15	TAGCCCTGCTGGTC
1611	PKA-16	CGCTTGGCGAAACC
1612	PKA-17	CCTTCACGCGCTTG
1613	PKA-18	AAGGTCCAAGTGCG
1614	PKA-19	TGCCGCACAAGGTC
1615	IL-12alpha-1	GGTGAGGACCACCATTT
1616	IL-12alpha-2	GGGTGTCACAGGTG
1617	IL-12alpha-3	ATACCATCTTCTTCAGGG
1618	IL-12alpha-4	GGTGATACCATCTTCTTC
1619	IL-12alpha-5	CCAGGTGATACCATCTTC
1620	IL-12alpha-6	CCTCACTGCTCTGGT
1621	IL-12alpha-7	TAAGACCTCACTGC
1622	IL-12alpha-8	CAGAGCCTAAGACCTC
1623	IL-12alpha-9	CCAGAGCCTAAGACC
1624	IL-12alpha-10	TCTTCCTTTTTGTGAAGC
1625	IL-12alpha-11	GACCAAATTCCATCTTCC
1626	IL-12alpha-12	ATCAGTGGACCAAATTCC
1627	IL-12alpha-13	GGTTCTTTCTGGTCCTTT
1628	IL-12alpha-14	TTTTTGGGTTCTTTCTGG
1629	IL-12alpha-15	GGTCTTATTTTTGGGTTC
1630	IL-12alpha-16	AATGGGCAGACTCTCCT
1631	IL-12alpha-17	TCCACCATGACCTCAATG
1632	IL-12alpha-18	AACGGCATCCACCATG
1633	IL-12alpha-19	GTGAACGGCATCCAC
1634	IL-12alpha-20	ACTTGAGCTTGTGAACGG
1635	IL-12alpha-21	TTCATACTTGAGCTTGTG
1636	IL-12alpha-22	CTGGTGTAGTTTTCATAC
1637	IL-12alpha-23	AGCTGCTGGTGTAGTTTT
1638	IL-12beta-1	AGGAGGACCAGGGT
1639	IL-12beta-2	AGGTGGTCCAGGAG
1640	IL-12beta-3	TTTCTGGCCAAACTGAGG
1641	IL-12beta-4	GGAGGTTTCTGGCC

Fig. 5 - 9

1642	IL-12beta-5	TCTGGAGTGGCCAC
1643	IL-12beta-6	CTTCTGGAGCATGTTGCT
1644	IL-12beta-7	GCCTTCTGGAGCATG
1645	IL-12beta-8	GTTTGTCTGGCCTTCTG
1646	IL-12beta-9	GAGTTTGTCTGGCCTTCT
1647	IL-12beta-10	CTAGAGTTTGTCTGGCCT
1648	IL-12beta-11	GCAAGGGTAAAATTCTAG
1649	IL-12beta-12	AGTGCAAGGGTAAAATTC
1650	IL-12beta-13	AAACAGGCCTCCACT
1651	IL-12beta-14	CTTGGTTAATTCCAATGG
1652	IL-12beta-15	AGGCAACTCCCATTAGTT
1653	IL-12beta-16	TACTACTAAGGCACAGGG
1654	IL-12beta-17	AATACTACTAAGGCACAG
1655	IL-12beta-18	GTACATCTTCAAGTCTTC
1656	Pg-R	GGAGTGGACATGAT
1657	thr	AAGAAGATGAAGCCTTTG
1658	ref-fosjun	CCGTCTTACTCTTCTTGG
1659	PIV	CCGATACAATTCCAAGG
1660	PIV	CCTTTTCCTTCTGAG
1661	PIV	CTGTTGCAAGTACG
1662	bak	CAGAAGCAGAGGGC
1663	bak	CCTCAGAAGCAGAGG
1664	bak	CTCCTCAGAAGCAG
1665	bak	ACAGGCTGGTGGCA
1666	bak	CCACTCTCAAACAGGC
1667	bak	ACGGTAGCCGAAGC
1668	bak	GACGGTAGCCGAAGC
1669	bak	GGCCAGACGGTAGC
1670	bak	GTGTAGGGCCAGACGGTA
1671	bak	CCGAAGCCATTTTTCAGG
1672	bak	CCCCGAAGCCATTTTTC
1673	bak	GGTTGATGTCGTCC
1674	bax	GCTTGAGACACTCGC
1675	bax	CCGGACCCGTCCAT
1676	bclx	GCTTGCTTTACTGC
1677	bclx	GGTTGCTCTGAGAC
1678	bclx	GCCACAGTCATGCC
1679	bmp	CGGGCATGCTGGCG
1680	bmp	GTGAAGTTCAGGATGATC
1681	bmp	CCAGTGCCTCATGG
1682	ICE	CAGTGTTCTCCATGG

Fig. 5 - 10

1683	ICE	CTGTACCAGACCGAG
1684	ICE	GCATACTGTTTCAGC
1685	ich	GCCATCAGCTCCTTG
1686	ich	CCACACCATAGATGG
1687	ich	GCTGGAGCAGTTTCC
1688	bcl1	CTCGCTTCTGCTGC
1689	bcl2	ACCGTGGCAAAGCG
1690	mucrep	AGGTGACACCGTGG
1691	AHR	GACTTGATTCCTTCAG
1692	AHR	GGATTTGACTTGATTCC
1693	AHR	GCTGCTGTTCATGG
1694	AHR	CCGTTTCTTTCAGTAGG
1695	CD2	CTTGAAGTAGGAGC
1696	MEK2	CGCTCCTACATGGC
1697	tnf	GATGAGGTACAGGCC
1698	tnf	GTAGATGAGGTACAG
1699	tnf	GAGTAGATGAGGTAC
1700	tnf	CCTGGGAGTAGATG
1701	tnf	GGACCTGGGAGTAG
1702	tnf	ACATGGGTGGAGGG
1703	tnf	GTGCTCATGGTGTC
1704	tnf	CTTTCAGTGCTCATG
1705	tnf	TGCTTTCAGTGCTCA
1706	tnf	GATGATCTGACTGCC
1707	tnf	GTTCGAGAAGATGATC
1708	tnf	GGGTTCGAGAAGATG
1709	tnf	GGTTTGCTACAACATG
1710	tnf	CAGCTTGAGGGTTTG
1711	tnf	TGCCCCTCAGCTTG
1712	TNFR	GACACACACTATCTC
1713	IL-18	GCAGCCATCTTTATTC
1714	IL-18	GTTCAGCAGCCATC
1715	IL-18	TGGTTCAGCAGCCA
1716	IL-18	CTACTGGTTCAGCAGC
1717	IL-18	TCTACTGGTTCAGC
1718	IL-18	GCCACAAAGTTGATGC
1719	IL-18	CATTGCCACAAAGTTG
1720	IL-18	GAGAACTTGGTCATTC
1721	IL-18	GGTCAATGAAGAGAAC
1722	IL-18	CGATTTCCTTGGTC
1723	IL-18	CCGATTTCCTTGGTC

Fig. 5 - 11

1724	IL-18	CAAATAGAGGCCGATTTC
1725	IL-18	CAAATAGAGGCCGA
1726	IL-18	CCTCTAGGCTGGCT
1727	IL-18	CATACCTCTAGGCTG
1728	IL-18	AGCCATACCTCTAG
1729	IL-18	CAGCCATACCTCTAG
1730	IL-18	CACAGAGATAGTTACAG
1731	IL-18	GTCTTCGTTTTGAACAG
1732	IL-18	CTAGTCTTCGTTTTGAAC
1733	IL-18	TAGCTAGTCTTCGTTTTG
1734	IL-18	GAGCCACTGCGCC
1735	IL-18	CGTGAGCCACTGCG
1736	IL-12-Rec	CGTAACGATCACTGG
1737	IL-12-Rec	GCACTCGTAACGATC
1738	IL-12-Rec	GGAGCACTCGTAAC
1739	IL-12-Rec	CATCATCCTGAGGT
1740	IL-12-Rec	CAGTATCATCATCCTG
1741	IL-12-Rec	CTCAGTATCATCATCC
1742	IL-12-Rec beta2	CTAAAAGTATGTGCCATC
1743	IL-12-Rec beta2	CACATCGCCTCTCT
1744	IL-12-Rec beta2	GCTTCACAGTCACATCGC
1745	IL-12-Rec beta2	GGAAGGCTTCACAGTC
1746	IL-12-Rec beta2	CCTGTGACTTGAGAATTG
1747	IL-12-Rec beta2	GGAAGACCTGTGAC
1748	IL-12-Rec beta2	CTCTGCTCCACATATTTG
1749	IL-12-Rec beta2	CAACGAAGATCTCTG
1750	IL-12-Rec beta2	CAACACCAACGAAG
1751	PKC-beta	GGTCTTCTGTTTGC
1752	CB-1-Rec	CGATGAAGTGGTAGGAAG
1753	TGF-alpha	GGTTGCATGGAAGC
1754	Fascin	GGTCACAAACTTGCC
1755	p300	CTGATTTGGTCCACTAG
1756	CBP	CATGTTAGCACTGTTC
1757	rac-alpha	GGTCTTGATGTACTCC
1758	EBV	CCACCTAAAGAGAGATC
1759	HSPQ	CTTGTACTGCACCATC
1760	CC-CKR1	GCCAGTTAAGAAGATG
1761	CC-CKR4	GAGATCATGATCCATGG
1762	c-CRK	GTAGTGTCCCAATAGTG
1763	c-CRK	CTTCCTCATCATTCCC
1764	CRKL	CACAAGCTTTTCGAC

Fig. 5 - 12

DECLARATION AND POWER OF ATTORNEY U.S.A.

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ALL PATENTS INCLUDING DESIGN
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As a below named inventor, I declare that my residence, post office address and citizenship are stated below next to my name; the information given herein is true; that I believe that I am the original, first and sole inventor (if only one name is listed at 201 below) or a first and joint inventor (if plural inventors are named below at 201-203 or on additional sheets attached hereto) of the subject matter which is claimed and for which patent is sought on the invention entitled

101 An antisense oligonucleotide preparation method

102 which is described and claimed in
the attached specification
X PCT International Application No. PCT/EP 98/00497 filed January 30, 1998
the specification in application Serial No. ____________ filed ____________
(if applicable) and amended on ____________

I hereby state that I have reviewed and understand the contents of the above-identified specifications, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to patentability as defined in Title 37, Code of Federal Regulations, §1.56.

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103

Prior Foreign Application(s) (Number)	(Country)	(Day/Month/Year Filed)	Priority Claimed Yes	No
97 101 531.8	Europe	31/01/1997	XX	

I hereby claim the benefit under Title 35, United States Code, §120 of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code, §112, I acknowledge the duty to disclose information which is material to patentability as defined in Title 37, Code of Federal Regulations, §1.56 which became available between the filing date of the prior application and the national or PCT international filing date of this application.

104

(Application Serial No.)	(Filing Date)	(Status: patented, pending, abandoned)

POWER OF ATTORNEY: As a named inventor, I hereby appoint the following attorneys (Registration No.) to prosecute this application, receive and act on instructions from my agent, and transact all business in the Patent and Trademark Office connected therewith. HARVEY B. JACOBSON, JR. (20,851); D. DOUGLAS PRICE (24,514); JOHN CLARKE HOLMAN (22,769); MARVIN R. STERN (20,640); MICHAEL R. SLOBASKY (26,421); JONATHAN L. SCHERER (29,851); STANFORD W. BERMAN (17,909); IRWIN M. AISENBERG (19,007); WILLIAM E. PLAYER (31,409)

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SIGNATURE OF INVENTOR 201*	SIGNATURE OF INVENTOR 202*	SIGNATURE OF INVENTOR 203*
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DATE 01. Sept 1999	DATE Sept 9th, 1999	DATE

*Additional inventors are named on separately numbered sheets attached hereto.

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